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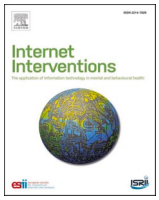

Guided internet-based cognitive-behavioral therapy for patients with chronic pain: A meta-analytic review

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ABSTRACT

Background: Chronic pain has a large individual and societal burden. Previous reviews have shown that internet-based cognitive-behavioral therapy (iCBT) can support patients' pain coping. However, factors related to participant experience of iCBT and effective and safe iCBT delivery for chronic pain have not recently been summarized.
Objective: The aim of this review was to give an overview of the efficacy of guided iCBT for chronic pain on psychological, physical, and impact on daily life outcomes, including factors that inform optimal delivery.
Methods: Cochrane, Emcare, Web of Science, PubMed, PsycINFO, and Embase were systematically searched from inception to 11 February 2022. Randomized controlled trials on guided iCBTs for adults with chronic pain were included with a broad range of outcomes.
Results: The search yielded 7406 studies of which 33 studies were included totaling 5133 participants. ICBT was more effective than passive control conditions for psychological (ES = 0.34–0.47), physical (ES = 0.26–0.29), and impact outcomes (ES = 0.38–0.41). ICBT was more effective than active control conditions for distress (ES = 0.40), pain acceptance (ES = 0.15), and pain interference after outlier removal (ES = 0.30). Longer treatments were associated with larger effects for anxiety and quality of life than shorter treatments. Mode of therapist contact (synchronous, asynchronous or a mix of both) was not related to differences in effect sizes in most outcomes. However, studies with mixed and synchronous contact modes had higher effects on pain self-efficacy than studies with asynchronous contact modes. Treatment satisfaction was high and adverse events were minor. Dropout was related to time, health, technical issues, and lack of computer skills.
Conclusions: Guided iCBT is an effective and potentially safe treatment for chronic pain. Future research should more consistently report on iCBT safety and detail the effectiveness of individual treatment components to optimize iCBT in clinical practice.

1. Introduction

Chronic pain is a complex condition with biological, psychological, and social factors playing a role in its development and maintenance (Goldberg and McGee, 2011). The condition can be defined as pain persisting longer than three months (Treede et al., 2015). It affects approximately 20 % of adults globally, although exact estimates are difficult to make (Goldberg and McGee, 2011). Chronic pain is associated with impaired physical (e.g., fatigue, diminished physical functioning), psychological (e.g., depression, anxiety) and social functioning (e.g., less social contact, job loss), thereby impacting the individual and society to a large extent (Dueñas et al., 2016). Treatment of chronic pain has shown to be challenging, with current pharmacological treatments proving to be only moderately effective at best (Turk et al., 2011). Improving capacities of patients in managing their condition ('self-management') is increasingly recognized as crucial in the

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treatment of chronic pain (Bodenheimer et al., 2002). Cognitive-behavioral therapy (CBT) has proven effective in supporting self-management of chronic pain patients, by focusing on dealing with dysfunctional beliefs and maladaptive behavioral patterns related to their condition (Dures and Hewlett, 2012; Ehde et al., 2014). However, patients suffering from chronic pain experience several barriers concerning traditional in-clinic CBT programs, such as reduced mobility due to physical complaints, limited transport possibilities, treatment costs, and associated stigma (Ehde et al., 2014; Jerant et al., 2005). Moreover, available therapists that provide CBT aimed at chronic pain are relatively limited (Ehde et al., 2014).

Internet-based CBT (iCBT) could largely bypass the barriers to face-to-face therapy, by offering an online self-management program that can be completed at home. Often the online treatment program consists of several themed modules or parts that can be worked on on a weekly basis, such as 'mood' and 'activities', while each module can be organized by components, such as goal-setting, psycho-education, assignments, registrations, relaxation exercises, and relapse prevention (Andersson et al., 2014; van Beugen et al., 2014). It can be offered in an unguided format in which patients work on online modules themselves, in some cases receiving automated messages, or in a guided format in which patients work on (tailored) online modules with the guidance of a therapist. In guided iCBT, generally a psychologist or coach provides the patient with written feedback on assignments following an intervention protocol and has a motivating role to increase adherence to the treatment (Andersson and Cuijpers, 2008).

Several domains that could inform efficient design and delivery of iCBT in chronic pain have been summarized by the Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials (IMMPACT; Turk et al., 2003; Dworkin et al., 2005). IMMPACT recommended that the following outcome domains should be taken into account when designing clinical trials on chronic pain: (1) pain, (2) physical functioning, (3) emotional functioning, (4) participant ratings of global improvement and treatment satisfaction, (5) participant disposition (e.g., dropout assessment), and (6) adverse events and symptoms (Turk et al., 2003; Dworkin et al., 2005). The first three outcome domains appear to be frequently reported in meta-analyses on internet-based interventions in chronic pain, whereas the last three domains related to participant experience and safety of the treatment are often not or only partly reported (Buhrman et al., 2016; Martorella et al., 2017; Vugts et al., 2018). ICBT interventions for mental health and chronic somatic (pain) conditions are found to be equally effective when compared to face-to-face CBT for a broad range of psychological and physical outcomes (Andersson et al., 2014; Bendig et al., 2018; Carlbring et al., 2018) and are generally more effective than passive control conditions (e.g., waitlist or care-as-usual) (van Beugen et al., 2014; Buhrman et al., 2016; Martorella et al., 2017; Vugts et al., 2018; Karyotaki et al., 2021). Specifically, internet-based (CBT) interventions for chronic somatic (pain) conditions are found to be more effective than passive control conditions for outcomes such as pain intensity, fatigue, pain-related interference/disability, pain acceptance, health-related quality of life, distress, depression, anxiety, and catastrophizing (van Beugen et al., 2014; Buhrman et al., 2016; Martorella et al., 2017; Vugts et al., 2018; Gandy et al., 2022). Additionally, guided internet-based interventions have shown larger effects than unguided internet-based interventions for mental health conditions (Karyotaki et al., 2021; Richards and Richardson, 2012; Baumeister et al., 2014). In chronic pain and other somatic health conditions, some meta-analyses showed superiority of guided internet-based interventions and others found similar effects of guided and unguided internet-based interventions (Buhrman et al., 2016; Vugts et al., 2018; Gandy et al., 2022; van Gils et al., 2016; Mehta et al., 2019; White et al., 2022). For example, a meta-analysis on iCBT in chronic health conditions found slightly stronger effects for guided interventions than for unguided interventions in reducing anxiety and depression symptoms (Mehta et al., 2019). In another previous meta-analysis on internet-based interventions for chronic pain (Buhrman et al., 2016), guidance was not found to be a significant moderator of treatment effects, although the number of included unguided studies was limited. The quality of the therapeutic relationship has shown to be directly related to clinical outcomes in guided iCBT (Ferwerda et al., 2016; Pihlaja et al., 2017). However, little is known about the relationship between the quantity of therapist contact and clinical outcomes in guided iCBT (Baumeister et al., 2014). Moreover, it is yet unknown whether a synchronous mode of therapist contact (e.g., via telephone), an asynchronous mode of contact (e.g., via e-mail) or a mix of asynchronous and synchronous modes of therapist contact in iCBT is more effective. More research on mode of therapist contact can show to what extent it can affect treatment outcomes and inform the optimal use of therapist contact within current and new iCBT treatments. Research on the influence of treatment duration on outcomes of iCBT has shown somewhat mixed results in mental health and chronic somatic (pain) conditions (van Beugen et al., 2014; Vugts et al., 2018; Păsărelu et al., 2017). A meta-analysis on iCBT (mostly involving therapist guidance) for depression and anxiety found that longer treatments (six modules or more) were associated with larger effects on depression outcomes compared to shorter treatments (less than six modules) when iCBT was compared to different control groups (Păsărelu et al., 2017). However, in within-group analyses of iCBT in the same meta-analysis, shorter treatments were associated with larger effects on depression and quality of life compared to longer treatments (Păsărelu et al., 2017). A different meta-analysis involving predominantly guided iCBT (next to other computer-based interventions) for chronic pain and functional somatic syndromes found no significant moderation effects for treatment duration (Vugts et al., 2018). Another meta-analysis on guided iCBT for chronic somatic conditions showed greater effects of iCBT on depression symptoms in interventions with a duration longer than 6 weeks as compared to treatments of 6 weeks or less when iCBT was compared to passive control conditions (van Beugen et al., 2014).

A recently published meta-analysis on guided and unguided iCBT in chronic pain (Gandy et al., 2022) reported significant small to medium effects for interference/disability, depression, anxiety, pain intensity, self-efficacy and pain catastrophizing when guided and unguided iCBT were compared to active and passive control conditions. Therapist guidance was found to moderate effects, with guided studies showing larger effects on interference/disability, anxiety, and pain intensity than unguided studies. Another significant moderator involved the type of control group (passive control conditions had greater effects on depression than active control conditions). However, the potentially important role of treatment duration and mode of therapist contact (synchronous, asynchronous, or mixed) has not been researched in the aforementioned meta-analysis (Gandy et al., 2022). Besides, several relevant IMMPACT-recommended outcome domains on participant experience and the safety of the treatment have not been included in this meta-analysis (Gandy et al., 2022), namely, participant ratings of overall improvement and treatment satisfaction, reasons for dropout as part of the participant disposition domain, and adverse events and symptoms (or negative treatment effects) (Turk et al., 2003; Dworkin et al., 2005). Also, iCBT has previously found to be effective for a broader range of treatment outcomes for chronic somatic (pain) conditions than included in the previously mentioned meta-analysis (Gandy et al., 2022) (e.g., for fatigue, distress, pain acceptance, quality of life; van Beugen et al., 2014; Vugts et al., 2018). Next, the previous meta-analysis did not analyze the results of guided iCBT compared to active and passive control conditions separately (Gandy et al., 2022). Singling out the effect of guided interventions compared to active control conditions on the one hand and passive control conditions on the other hand, could result in concrete recommendations for clinical practice considering this treatment form. Finally, the aforementioned meta-analysis included studies that compared iCBT to an active control condition when a passive control condition was also present but did not include studies that compared iCBT to an active control condition only. Including studies that directly compare iCBT to active control conditions could result in further

concrete indications for implementation of interventions in clinical practice. Hence, in order to guide intervention development and facilitate clinical application of guided iCBT for chronic pain, an updated overview of the efficacy of guided iCBT for this condition is needed for a broad range of outcomes and control conditions. Since therapist guidance has shown to be beneficial, the current meta-analysis aims to investigate whether guided iCBT can be effective for chronic pain and for which psychological, physical, and impact on daily life outcomes it may be effective (such as distress, pain acceptance, pain intensity, fatigue, and quality of life). A second aim is to gain a better understanding on factors that inform an effective and a safe delivery of the treatment. Specifically, domains of interest are the involvement of the therapist, treatment duration, global improvement and participant satisfaction with the treatment, the extent of and reasons for treatment dropout, and adverse events and negative treatment effects in order to give indications for optimizing iCBT delivery.

2. Materials and methods

2.1. Protocol and registration

The research protocol for the meta-analytic review is registered with the International Register of Prospective Reviews (PROSPERO); the registration number is CRD42017079422. Minor amendments to the protocol were made that corrected a spelling mistake and the anticipated completion date of the review. The last protocol amendment that is still under review included an updated literature search and author list, and clarifications in the methods section (further details will be published on PROSPERO). The review followed PRISMA guidelines (Page et al., 2021a). Data collection forms, extracted data from included studies in this review, and data used for statistical analyses are available from the corresponding author on request.

2.2. Search strategy

A first search for published studies was conducted from inception to 11 February 2022, using Cochrane, Emcare, Web of Science, PubMed, PsycINFO, and Embase. Index terms indicative of effect studies, such as 'cognitive-behavioral therapy', 'internet' and 'chronic pain', were combined. Additionally, Medical Subject Heading (MeSH) terms, such as 'online', 'electronic mail', 'pain', 'internet', 'rehabilitation', and 'behavior therapy', were used (see Supplemental Digital Content, Appendix A for full search description). To save and categorize the results into different thematic libraries, the online version of Endnote (Endnote web) was used. First, to select candidate studies for inclusion, a rater (MV) screened titles and abstracts without blinding to journal or authorship. Second, two raters (JT and MV) investigated the full text of candidate studies and saved studies that met inclusion criteria in a separate Excel file. Inconsistencies in inclusion were resolved by discussion with a third review team member (AE). Lastly, two raters (JT and MV) independently screened references in eligible articles for relevant studies. Cohen's kappa was calculated to describe the agreement between the raters.

2.3. Eligibility criteria

The inclusion criteria for the selection of the articles were: (1) participants of 18 years and older who experienced chronic pain (i.e., patients had pain lasting a minimum of 3 months and/or were diagnosed with a condition of which chronic pain was a primary feature, such as rheumatoid arthritis and fibromyalgia); (2) randomized controlled trial (RCT) or equivalence trial in which iCBT was compared with a control condition; (3) available in English language; (4) access to the full text of the article; (5) contained outcome variable on pain (e.g., pain coping, pain intensity) to include studies with a clear focus on pain as opposed to lifestyle change (see exclusion criteria); (6) therapy mainly provided through the internet (i.e., patients spent >50 % of the total intervention time using an online intervention; no telephone calls or videoconferencing only, no onsite computerized therapy or digital assistants); (7) CBT-based therapy in which a minimum of two forms of cognitive and/or behavioral techniques were used (e.g., cognitive restructuring and activity scheduling); and (8) therapist-guided, with a minimum of one segment of personalized patient contact to foster treatment adherence and/or provide feedback (either through messages or another mode of contact, excluding technical support with IT problems). The exclusion criteria were: (1) the primary goal of the intervention was lifestyle change with a main focus on improving health behaviors (e.g., a focus on weight loss or exercise only) or the study was focused on monitoring symptoms, (2) pain was not a primary feature of the conditions investigated in the study, (3) the study contained <20 study subjects per study arm, and (4) the paper did not use original data. Potentially eligible studies were screened using a screening hierarchy (see Supplemental Digital Content, Appendix B). When a study would be excluded based on a criterion, it would not be screened for the remaining criteria of the screening hierarchy. The PRISMA flow diagram in Fig. 1 depicts the paper inclusion process.

2.4. Data extraction

A member of the review team (IG) conducted the first data extraction. Subsequently, a second review team member (JT) independently collected data from a random sample of the included studies to check for accuracy. For each of the included studies, the following data were gathered: publication year, location of data collection, recruitment type (e.g., hospital or media advertisements), number of patients included in control and intervention groups, sex and age of included patients, type of chronic pain condition, inclusion/exclusion criteria (pain duration as inclusion criterion or not), average pain duration, type of control condition, completer or intent-to-treat analyses, length and type of follow-up, intervention content and duration, therapy provider (e.g., psychologist or psychiatrist), whether therapy provider is trained in CBT, mode, frequency and duration of therapist contact, patient satisfaction with treatment, participant rating of global improvement, number of dropouts and dropout reasons, adverse events and negative treatment effects, treatment deterioration, whether groups were comparable at baseline, post-treatment results, and follow-up results. Finally, three outcome categories related to chronic (pain) conditions (van Beugen et al., 2014) were extracted: (1) psychological outcomes (e.g., depression symptoms and anxiety symptoms), (2) physical outcomes (e.g., pain intensity), and (3) impact of pain on daily life outcomes (e.g., quality of life). When outcomes would fall into one of these outcome categories but could not be pooled (e.g., due to a lack of studies), these were not included in the meta-analysis. When a study reported on more than one measurement instrument for the same outcome, either the most comparable instrument to those included in other studies or the most validated instrument was considered for the analysis.

2.5. Risk of bias

Two raters (JT and IG) independently assessed each study for risk of bias throughout the six domains of the Cochrane Collaboration tool (Higgins et al., 2011): (1) randomization sequence for allocation to conditions, (2) concealment of allocation to a condition before and until assignment to a condition, (3) blinding of outcome assessment (blinding of outcome assessors including blinding of the statistician, e.g., blind assessment of clinician-reported measurements and blind data analysis), (4) handling of missing data, (5) systematic differences in dropout between groups, and (6) other bias. A third rater (AE) was involved to resolve any inconsistencies between the two raters. Within each study, the raters assessed whether there was a high risk of bias (−), an unclear risk of bias (?), or a low risk of bias (+) for each domain of potential bias.

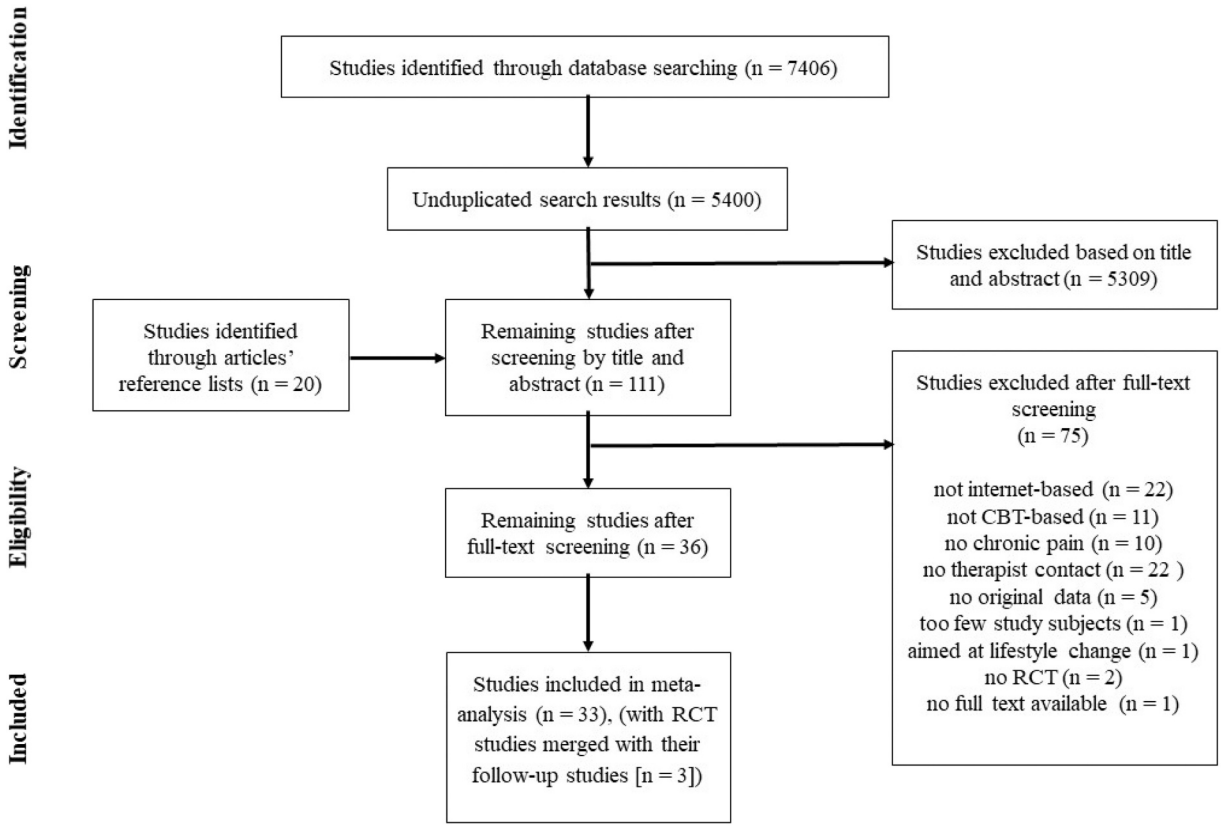

Fig. 1. PRISMA flow diagram of study selection.

2.6. Data synthesis

When possible (i.e., whenever an outcome contained at least two studies), between-group results were pooled to study the effect of iCBT as compared to a passive control condition on the one hand or an active control condition on the other hand. Passive control conditions entailed waiting lists, standard care, or intervention programs that were not expected to substantively affect any therapeutic outcomes (van Beugen et al., 2014). Active control conditions were interventions in which participants attended a therapeutic program that was expected to affect therapeutic outcomes (e.g., face-to-face CBT or a different psychotherapy). In three-arm studies where iCBT was compared to a passive and an active control condition, the study would be included in two analyses (iCBT versus a passive control condition and iCBT versus an active control condition). When a study contained multiple iCBT treatment groups and a passive control condition, the iCBT treatment group with the most therapist contact was compared to the iCBT treatment with the least therapist contact in one analysis and the iCBT treatment group with the most therapist contact was compared to a passive control condition in another analysis. Pooling of between-group follow-up results was not possible, due to a lack of uniform reporting of these results across studies (follow-up periods differed greatly, some studies aggregated results from treatment and control groups in follow-up, and other studies only reported a follow-up for the treatment group). Thus, only post-intervention results were quantitatively summarized. Dropouts were calculated separately for all conditions (iCBT, passive, and active control). Dropouts were defined as participants that dropped out of the intervention or control condition and/or participants that did not return post-treatment measurements.

2.7. Data analyses

Comprehensive Meta-Analysis v.3 software was used for all analyses except power analyses for which R statistical computing software was used (Quintana, 2017). The standardized mean difference (SMD), which calculates the intervention effect relative to the variability in the study, was used as a measure of effect size. The formulas for effect size calculations and pooling of effect sizes have been added to Supplemental Digital Content, Appendix K. Effect sizes were categorized as small (0.2), medium (0.5) or large (0.8) (Cohen, 1988). Mean values and standard deviations for the intervention and control groups were extracted from their respective articles. In case of missing data, authors were contacted to retrieve data. Authors of all studies were contacted to request additional information. Information was requested when data were missing concerning study characteristics, risk of bias, participant ratings of global improvement and satisfaction with treatment, adverse events and negative treatment effects, clinical deterioration, and standard deviations for mean values or interquartile ranges for median values. Authors of fifteen studies provided additional information upon request (e.g., Dear et al., 2013; Friesen et al., 2017; Lorig et al., 2008; Peters et al., 2017; see Supplemental Digital Content, Appendix J, Table I). Authors of the remaining studies could not be reached or could not provide additional information (e.g., Bendelin et al., 2021; Buhrman et al., 2004, 2011, 2013, 2015; Shigaki et al., 2013). Of note, in one study, missing data concerning participant ratings of global improvement and satisfaction with treatment could not be retrieved and could therefore not be reported on (Lin et al., 2017). In two studies, missing standard deviations could not be retrieved (Scott et al., 2018; Rickardsson et al., 2021). Therefore, standard deviations were calculated from the 95 % confidence interval (Scott et al., 2018) or the standard error (Rickardsson et al., 2021) following recommendations from the Cochrane Handbook (Higgins and Green, 2011). To describe the heterogeneity in the included studies per outcome the I^2 index, which assesses the percentage of total variation between studies due to heterogeneity (Higgins et al., 2003), was computed. A broad distinction can be made between an I^2 of 25 % (low heterogeneity), 50 % (moderate heterogeneity), and

75 % (high heterogeneity) (Higgins et al., 2003). In case of high heterogeneity, the effect sizes differ across studies and the focus should shift onto the source of heterogeneity. As some heterogeneity is anticipated across studies, random-effects models were applied. These models assume that effect sizes vary between studies, estimating the mean from a distribution of effects (Kanters, 2022). SMDs were displayed in tables and forest plots. A sensitivity analysis was performed where outliers were removed and the impact on the overall effect size per outcome was reported. Outliers were detected by inspecting the 95 % confidence intervals of individual studies and assessing if they overlap with the 95 % confidence interval of the pooled effect size, with the use of forest plots. If the confidence interval of the effect size of a study did not overlap with the confidence interval of the pooled effect size, the effect size of that study differed abnormally from the pooled effect size and was thus considered an outlier (Harrer et al., 2021). Outliers were removed in the sensitivity analysis.

Meta-analyses using fixed-effects models have an increased power to detect effects compared to individual studies, but this is not necessarily true for meta-analyses using random-effects models due to allowing for between-study variance (Jackson and Turner, 2017). In meta-analyses using a random-effects model, retrospective power analysis can be useful to assess the likelihood that low statistical power has led to incorrect statistical conclusions (Valentine et al., 2010). Insufficient power could pose an alternative explanation for null-findings as opposed to the absence of effects. In this meta-analysis, retrospective power analyses were performed based on previously described recommendations (Valentine et al., 2010) for iCBT versus passive control conditions and iCBT versus active control conditions, for each outcome within the respective comparison group separately. The effects of iCBT on the outcomes were expected to be small, based on previous meta-analyses (van Beugen et al., 2014; Vugts et al., 2018), where comparisons with active control groups yielded smaller effects than comparisons with passive control groups (Vugts et al., 2018). Therefore, the power to detect an effect size of 0.30 for each outcome in the iCBT versus passive control comparison group was assessed and an effect size of 0.20 for each outcome in the iCBT versus active control comparison. Furthermore, a level of statistical significance of 0.05, moderate heterogeneity, $I^2 = 0.50$, and the observed overall group sizes and included studies per outcome were applied in the calculation. The desirable power threshold was 0.80, which indicates an 80 % probability of detecting a statistically significant effect of the desired magnitude when it is present. The code for power analyses (Quintana, 2017) was adapted from previous formulas (Valentine et al., 2010).

To assess publication bias, the funnel plot technique was applied using the standard error as a measure of effect size, Egger's regression test (Egger et al., 1997) was used and Duval and Tweedie's trim-and-fill procedure (Duval and Tweedie, 2000). Only outcomes that were assessed in 10 studies or more were included in the publication bias analysis because the statistical tests used for funnel plot asymmetry are underpowered when there are <10 studies per outcome (Page et al., 2021b). Finally, “treatment duration” was investigated as a potential moderator for the effect of iCBT on the outcome measures.

A linear meta-regression was performed for each outcome measure to assess treatment duration as a continuous moderator variable in iCBT versus passive control conditions and iCBT versus active control conditions. Only outcome measures that were included in a minimum of 10 studies were included in the meta-regression, based on previous recommendations (Higgins and Green, 2011). Regression plots were inspected for unusual observations. Studies with a high leverage (i.e., studies with a leverage that was at least twice as high as the average leverage (Hoaglin and Welsch, 1978)) were excluded in a secondary sensitivity analysis to rule out their effects on meta-regression results. Since therapist involvement (i.e., the total therapist time spent per participant) was not uniformly reported across studies, the amount of therapist involvement could not be investigated as a potential moderator of iCBT effects and results were narratively summarized. Finally, the main mode of therapist contact (e.g., telephone calls or e-mails), was exploratively investigated as a moderator of treatment effects. Each main mode of contact was evaluated as being synchronous (i.e., contact between therapist and patient in real-time), asynchronous (i.e., contact between therapist and patient not in real-time), or a mixture of synchronous and asynchronous contact. The effect sizes of the three groups (synchronous, asynchronous, or mix), were compared by performing post-hoc mixed-effects subgroup analyses using at least three studies per group for every outcome. Analyses were performed again in sensitivity analyses where outlying studies, identified in the main meta-analyses, were removed from the subgroup analyses. When the subgroup analysis showed a significant overall result, a categorical meta-regression would be performed to inspect the differences between the groups.

3. Results

3.1. Search results and study characteristics

The search and selection procedures are summarized in Fig. 1. The database search resulted in 7406 potentially relevant articles of which 5400 were unduplicated search results. After screening titles and abstracts, 5309 studies were excluded. Subsequently, 111 studies were included in the full-text screening, which encompassed 20 additional studies that were identified through articles' reference lists. A total of 36 articles fulfilled all inclusion criteria. Three of the included studies were long-term follow-up studies (Ljótsson et al., 2011; Kristjánsdóttir et al., 2013a; Dear et al., 2018), which were merged with the publications that reported the pre- and post-intervention measurements of the same data set (Ljótsson et al., 2010; Kristjánsdóttir et al., 2013b; Dear et al., 2015). Thus, 33 separate studies were included in the meta-analysis. Interrater reliability indicated a high agreement between raters (Cohen's $\kappa = 0.918$).

The study characteristics are reported in Supplemental Digital Content, Appendix C. The studies were published between 2003 and 2022. The interventions were conducted in Sweden (10/33, 30 %), Australia (6/33, 18 %), The Netherlands (4/33, 12 %), Germany (4/33, 12 %), the United States of America (3/33, 9 %), Canada (2/33, 6 %), Norway (1/33, 3 %), Ireland (1/33, 3 %), the United Kingdom (1/33, 3 %), and Spain (1/33, 3 %). Ten studies (30 %) recruited patients exclusively from hospitals or clinics, whereas 23 studies (70 %) recruited patients via a combination of media advertisements, contact with patient groups and clinics, and patient databases. The studies included a total of 5133 subjects (2340 in the intervention and 2793 in the active or passive control groups), with sample sizes ranging from 44 to 855 per study. Seventy-nine percent of the participants were female ($n = 4033$). The participants were on average 50 years of age (pooled mean) and the age range varied between 18 and 93 years. The conditions of patients encompassed mixed chronic pain syndromes (16/33, 48 %), chronic back pain (5/33, 15 %), fibromyalgia (4/33, 12 %), (rheumatoid) arthritis (2/33, 6 %), recurrent/chronic headache (2/33, 6 %), irritable bowel syndrome (1/33, 3 %), chronic knee pain (1/33, 3 %), hip osteoarthritis (1/33, 3 %), and chronic musculoskeletal pain (1/33, 3 %). Most studies (25/33, 76 %) had pain duration as an inclusion criterion, ranging from a minimum pain duration of 3 months to a minimum of 24 months.

Twenty-one studies compared iCBT with a passive control condition: waiting list (11/21, 52 %), care-as-usual (7/21, 33 %), or an educational intervention (3/21, 14 %), while seven studies compared iCBT with an active control condition: iCBT or online pain management without added telephone contact (2/7, 29 %), face-to-face CBT group intervention (1/7, 14 %), CBT (pain management) workbook (1/7, 14 %), hybrid emotion-focused treatment (1/7, 14 %), multimodal pain rehabilitation (1/7, 14 %) or a moderated online discussion forum with general pain-related topics (1/7, 14 %). Four studies used a three-arm design in which iCBT was compared with a passive waiting list control condition and with other interventions (i.e., internet-based positive psychology

intervention, expressive writing, face-to-face CBT, unguided internet-based acceptance and commitment therapy). One study used a four-arm design, which compared three intervention groups (iCBT with regular therapist contact, iCBT with optional therapist contact, and iCBT without contact) to a treatment-as-usual waiting list group.

3.2. ICBT content and duration

All interventions were based on CBT. In the studies, the interventions were labelled as iCBT (10/33, 30 %), acceptance and commitment therapy (ACT) (8/33, 24 %), self-management or self-help based on CBT (7/33, 21 %), pain management or pain coping skills training (6/33, 18 %), or exposure and mindfulness-based therapy (2/33, 6 %). The interventions mostly consisted of weekly modules with (homework) assignments and most often used multiple digital modalities within the same treatment (e.g., written text, video, and downloadable audio files; see Supplemental Digital Content, Appendix C). The interventions had a pooled average duration of 9 weeks (range 4 to 26 weeks) and applied a variety of CBT-based techniques. The most frequently mentioned intervention component was psychoeducation, which was used in all studies. Relapse prevention (25/33), self-monitoring (22/33), relaxation (22/33), goal setting (20/33), activity planning (19/33), cognitive restructuring (19/33), and problem solving (18/33) were used in more than half of the interventions.

3.3. Therapist guidance

In the iCBT interventions, the main mode of contact was e-mail or written feedback in 18 studies (55 %), a mix of different main contact modes (e.g., written feedback and telephone contact) in 8 studies (24 %), telephone calls in 4 studies (12 %), videoconference calls in one study (3 %), a bulletin board in one study (3 %), and face-to-face contact in one study (3 %). Six studies (18 %) used standardized SMS text messages (sometimes optional) to motivate participants for the treatment, repeat content, remind them of assignments or provide them with a link to registrations. Therapist guidance was most often provided by psychologists (27/33, 82 %), who had typically received a form of CBT training as professional qualification. Guidance was occasionally also provided by physiotherapists (9 %), a combination of a pain physiotherapist and a pain psychologist (3 %), a combination of a nurse and a therapist (3 %), and peer moderators (3 %). In 50 % of studies including therapist guidance by someone other than a psychologist, the included therapists had received CBT training (see Supplemental Digital Content, Appendix C). Eleven studies (33 %) reported the total therapist time for the entire duration of the treatment, which ranged from 41 to 174 min per participant per treatment.

3.4. Participant ratings of global improvement and satisfaction with treatment

Participant ratings of global improvement were assessed and reported in six studies (Scott et al., 2018; Kristjánsdóttir et al., 2013a; Bennell et al., 2018; Hedman-Lagerlöf et al., 2018; Boersma et al., 2019; Burke et al., 2019; shown in Supplemental Digital Content, Table A of Appendix D). After treatment, 34 % to 56.5 % of participants in intervention groups reported overall improvement, compared to 20 % to 58 % in the (passive) control groups (Scott et al., 2018; Bennell et al., 2018; Burke et al., 2019). After the iCBT intervention, three studies (Scott et al., 2018; Bennell et al., 2018; Hedman-Lagerlöf et al., 2018) found a significantly higher mean improvement rating in the intervention group than in the passive control group, and another study (Boersma et al., 2019) found a significantly higher mean improvement rating in the active control group than in the intervention group. At follow-up, 27 to 48 % of participants in intervention groups reported overall improvement, compared to 15 to 56 % in the (passive) control groups (Scott et al., 2018; Kristjánsdóttir et al., 2013a; Bennell et al., 2018; Burke et al., 2019).

Participants' satisfaction with treatment was assessed in 15 studies in varying ways (shown in Supplemental Digital Content, Table B in Appendix D). Participants were overall satisfied with treatment across studies, they would recommend the treatment and felt it was worth their time. Seven studies compared satisfaction with treatment between iCBT groups and active control groups. Five of these found no significant differences in satisfaction between the iCBT groups and active control groups (Lin et al., 2017; Dear et al., 2015; de Boer et al., 2014; Dear et al., 2017; Gardner et al., 2022). One study found that satisfaction with treatment was significantly higher among participants in the active control group (hybrid emotion-focused treatment) compared to the iCBT group (Boersma et al., 2019), and one study found that satisfaction with treatment was significantly higher among participants in the internet-based ACT group compared to the active control group (expressive writing) (Trompetter et al., 2015).

3.5. Dropout reasons

Twenty studies examined reasons for dropouts to a varying extent and reported different reasons for dropout. The most common reasons were lack of time, health issues/hospitalization, technical difficulties, and lack of computer skills. Dropouts for the iCBT conditions, the active control conditions, and passive control conditions, were calculated separately. The iCBT and active control conditions had similar dropout rates (both 23 %), whereas passive control conditions had slightly lower dropout rates (16 %). One study (Buhrman et al., 2004) only reported five dropouts but did not indicate to which study groups they belonged. In the dropout calculations, three of these were allocated to the intervention group and two to the control group.

3.6. Adverse events and negative treatment effects

Adverse events and negative treatment effects were assessed and reported in varying ways in 11 studies (shown in Supplemental Digital Content, Table C in Appendix E). Participants were usually prompted to report adverse events themselves, whereas negative treatment effects were assessed using questionnaires. Some studies defined adverse events as negative events related to the treatment, others reported any adverse event regardless of whether they were related to the treatment, and some studies only reported the absence of serious adverse events. Of the studies that reported adverse events, no serious adverse events were reported. However, some studies listed 'hospitalization' as a reason for (iCBT) dropout (Dear et al., 2017; Trompetter et al., 2015), which can be classified as a serious adverse event (Duggan et al., 2014). One of the most commonly reported adverse events within studies was increased pain (in iCBT and/or passive control groups; Bennell et al., 2018; Hedman-Lagerlöf et al., 2018; Bennell et al., 2017). Others included increased symptoms of a shoulder problem or leg spasms (iCBT group) (Burke et al., 2019), stress (iCBT group) and increased anxiety or depressive symptoms (active control group) (Boersma et al., 2019). The most commonly reported negative treatment effects were increased suffering due to past experiences (Sander et al., 2020; Schlicker et al., 2020) and more conflict in relationships (Sander et al., 2020; Baumeister et al., 2020). The proportion of participants showing deterioration (i.e., a worsening of symptoms) was calculated for different measures in seven studies. The proportion of participants showing deterioration in a specific measure in the intervention group ranged from 0 % to 13 %, which was a similar or smaller proportion than participants in the control groups (shown in Supplemental Digital Content, Table D in Appendix E).

3.7. Risk of bias assessment

Risk of bias assessments per study are presented in Figs. 2 and 3. Most studies (29/33, 88 %) reported adequate randomization methods and a minority (4/33, 12 %) reported unclear randomization methods. Also,

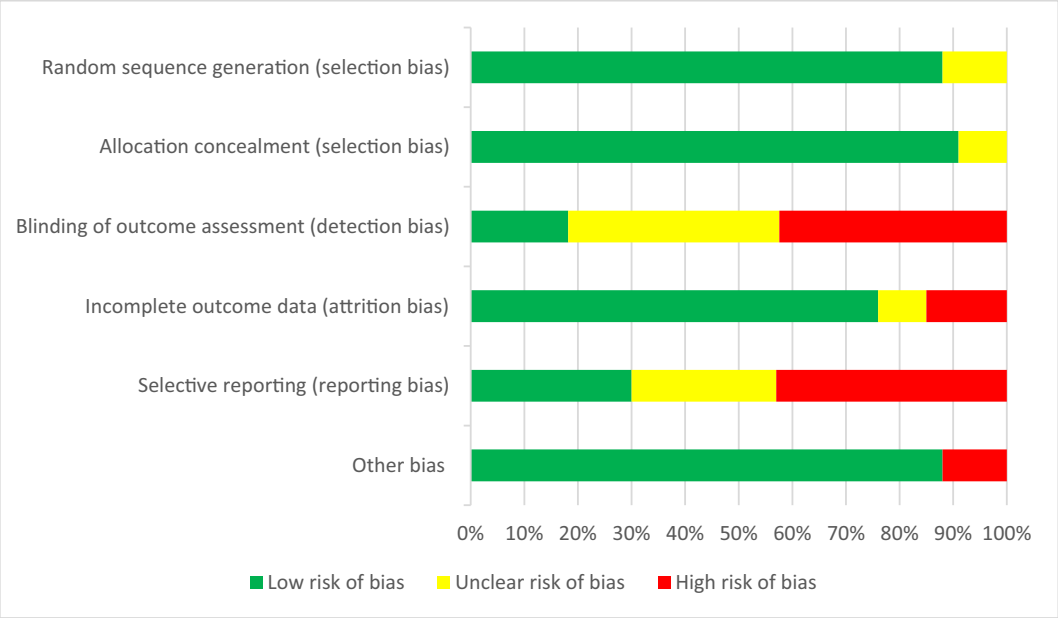

Fig. 2. Risk of bias graph.

91 % (30/33) of the studies adequately concealed the allocation sequence before and until assignment, while in the remaining studies (3/33, 9 %) allocation concealment was unclear. Thirteen studies (39 %) did not report blinding of outcome assessment (specifically no reported blinding of the statistician), which was considered an unclear risk of detection bias in these studies. In another 14 studies (42 %), the identity of participants or their allocation to a study group was not masked in outcome assessment (e.g., the study groups had assessment points at different time points and/or only the intervention group was included in the follow-up, or the statistician was not blinded), which was categorized as a high risk of detection bias. Only six (18 %) of the included studies adequately reported blinding of outcome assessments (i.e., blind assessment of clinician-reported measurements if these measurements were applied) including blinding of the statistician. Regarding risk of attrition bias, 25 studies (76 %) adequately handled the outcome data, which led to a low risk of attrition bias. These studies appropriately described dropouts, attrition, and handling of missing data following ITT principles. Three studies (9 %) insufficiently described outcome data, which led to an unclear risk of attrition bias. Five studies (15 %) were perceived to be at a high risk for attrition bias due to a lack of intention-to-treat analyses. The risk of selective reporting was low in only 10 studies (30 %), which were reported adequately in clinical trial registers. Another nine studies (27 %) had an unclear selective reporting bias, either because no registration in a clinical trial register could be found or because registration in a clinical trial register took place after the study was completed. Fourteen studies (42 %) were inadequately reported in clinical trial registers (mostly because not all outcome measures were reported beforehand) and were therefore evaluated as having a high risk of selective reporting bias. Other biases could not be detected in the majority of studies (29/33, 88 %). However, four studies (12 %) were evaluated as having a high risk of other biases because they had a limited sample size, which reduced power for the detection of effects, they did not statistically correct for cluster randomization, they asked for consent for participation after patients had been randomized, or they included a complicated comparison of individual online therapy versus face-to-face group therapy.

3.8. ICBT effectiveness compared to passive control conditions

Twenty-six studies compared iCBT with a passive control condition. Power analyses showed that the power threshold of 0.80 was reached for every outcome within the iCBT versus passive control comparisons (see Supplemental Digital Content, Appendix F). For the comparisons between iCBT and passive control conditions, pooled SMDs for the three outcome categories are shown in Table 1.

3.8.1. Psychological outcomes

The psychological outcomes that were assessed in the meta-analysis encompassed anxiety, depression, pain self-efficacy, catastrophizing, pain acceptance, and distress. Overall, iCBT had a larger positive effect than passive control conditions on all assessed psychological outcomes, with effect sizes ranging from small to medium for all outcomes (pooled SMDs = 0.34–0.47; see Table 1 and Supplemental Digital Content, Figs. 4–9 in Appendix G). Moderate to high heterogeneity in effect sizes was found for pain self-efficacy and distress, moderate heterogeneity for depression and anxiety symptoms, low heterogeneity for catastrophizing, and very low heterogeneity for pain acceptance. Several outliers were detected in the analyses for the psychological outcomes. When removing one outlier (Dear et al., 2015) from the analysis of the effect on depression, the pooled SMD decreased from 0.47 with moderate heterogeneity to 0.43 with low heterogeneity ($k = 22$, 95 % CI [0.34, 0.52], $z = 9.13, p < .001, I^2 = 18$ %). When removing one outlier (Bennell et al., 2018) from the analysis of the effect on catastrophizing, the pooled SMD increased from 0.43 with low heterogeneity to 0.48 with very low heterogeneity ($k = 11$, 95 % CI [0.36, 0.61], z = 7.40, $p < .001$, $I^2 = 0$ %). Lastly, when one outlier (Vallejo et al., 2015) was removed from the analysis of the effect on distress, the pooled SMD decreased from 0.43 with moderate to high heterogeneity to 0.33 with moderate heterogeneity ($k = 8$, 95 % CI [0.14, 0.52], $z = 3.46$, $p = .001$, $I^2 = 48$ %).

3.8.2. Physical outcomes

The analyzed physical outcomes consisted of pain intensity and fatigue. Overall, iCBT had a larger positive effect than passive control conditions on both physical outcomes, with pooled SMDs in the small range (pooled SMDs = 0.26–0.29; see Table 1 and Supplemental Digital Content, Figs. 10, 11 in Appendix G). Heterogeneity in effect seizes was moderate to high for both outcomes. Three outliers (Bennell et al., 2018; Hedman-Lagerlöf et al., 2018; Bennell et al., 2017) were detected in the analysis of the effects on pain intensity. Removing these outliers from the analysis decreased the pooled SMD for pain intensity from 0.29 with

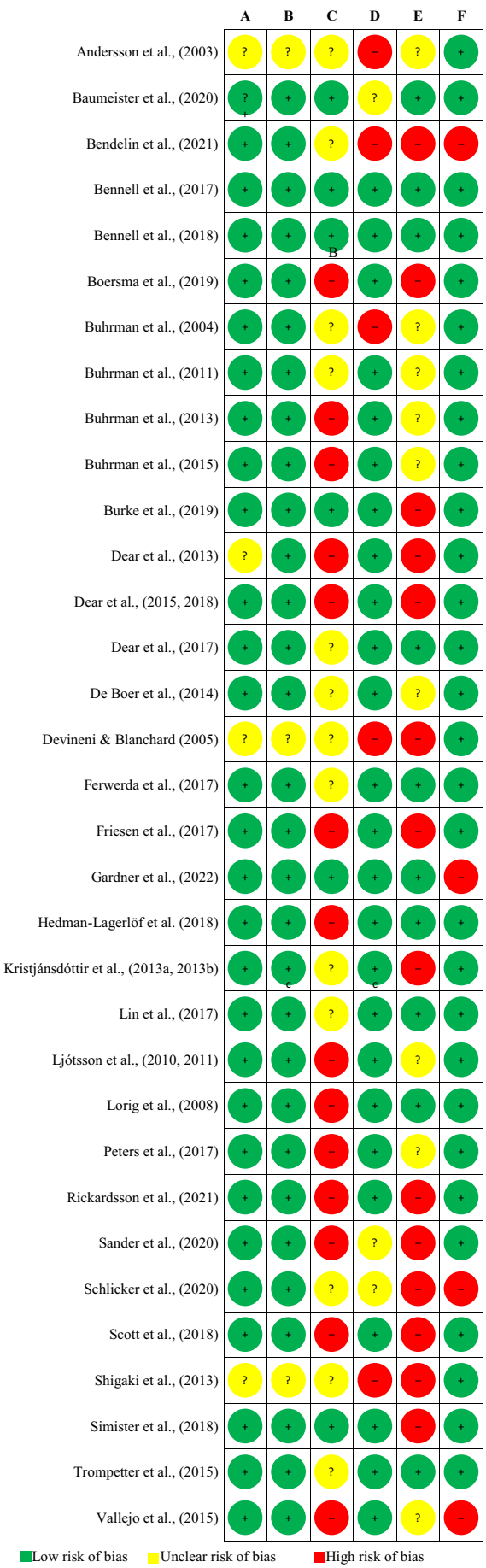

Fig. 3. Risk of bias summary: review authors' judgements for each included study about each risk of bias item. A = Random sequence generation (selection bias); B = Allocation concealment (selection bias); C = Blinding of outcome assessment (detection bias); D = Incomplete outcome data (attrition bias); E = Selective reporting (reporting bias); F = Other bias.

(caption on next column)

moderate to high heterogeneity to 0.27 with moderate heterogeneity (k = 21, 95 % CI [0.16, 0.38], z = 4.93, $p < .001$, I^2 = 46 %).

3.8.3. Impact on daily life outcomes

The assessed impact on daily life outcomes consisted of pain interference and quality of life. On average, the iCBT conditions had a larger positive effect on both pain interference and quality of life in comparison to passive control conditions with pooled SMDs in the small to medium range (pooled SMDs = 0.38–0.41; see Table 1 and Supplemental Digital Content, Figs. 12, 13 in Appendix G). Low to moderate heterogeneity in effect sizes was found for pain interference and moderate to high heterogeneity for quality of life. One outlier (Ljótsson et al., 2010) was detected in the analysis of the effects on quality of life. Removing this outlier from the analysis decreased the pooled SMD for quality of life from 0.38 with moderate to high heterogeneity to 0.33 with low to moderate heterogeneity (k = 11, 95 % CI [0.19, 0.47], z = 4.72, $p < .001$, I^2 = 35 %).

3.9. ICBT effectiveness compared to active control conditions

Twelve studies compared iCBT with an active control condition. The results per outcome for the iCBT versus active control comparisons are reported in Table 2 and Supplemental Digital Content, Figs. 14–21 in Appendix G. Analyses of effects on fatigue and quality of life were not possible, as each analysis only included one study. None of the analyses within the iCBT versus active control comparisons reached the power threshold of 0.80 (see Supplemental Digital Content, Appendix F) to detect a statistically significant pooled SMD of 0.20 if it exists. However, the pooled SMDs on depression, anxiety, catastrophizing, pain self-efficacy, and pain intensity were close to zero, suggesting that the difference in effects between iCBT and active control groups may be non-existent, rather than undetected due to insufficient power. A small difference was detected in the effects on pain acceptance (pooled SMD 0.15, k = 5, 95 % CI [0.01–0.29], p = .036, I^2 = 0 %), as well as a small to medium difference in effects on distress (pooled SMD 0.40, k = 5, 95 % CI [0.14–0.66], p = .002, I^2 = 18.96 %), both in favor of iCBT. After removing one outlier (Boersma et al., 2019) from the analysis of the effects on pain interference, the pooled SMD increased from a non-significant effect of 0.16 with high heterogeneity to a significant effect of 0.30 with very low heterogeneity in favor of iCBT (k = 6, 95 % CI [0.14–0.45], $p < .001$, I^2 = 0 %).

3.10. Moderation analyses

Linear meta-regressions were performed to investigate the potential role of treatment duration (in weeks) as a continuous moderator for the effect of iCBT compared to passive or active controls. An overview of treatment duration per study is given in Supplemental Digital Content, Table E in Appendix H. For the comparisons of iCBT to passive control conditions, the outcomes of depression, anxiety, catastrophizing, pain self-efficacy, pain intensity, and quality of life were reported in a minimum of 10 studies and therefore included in the meta-regression. There were two studies with considerably longer treatments (24 weeks [Bennell et al., 2018] and 26.07 weeks on average [Ferwerda et al., 2017]) compared to the treatments in the other 24 studies (ranging from 4 to 12 weeks). These studies consistently had high leverage, as characterized by at least twice the average observed leverage (Hoaglin and Welsch, 1978) and strongly affected the regression coefficients when they were included in analyses. Therefore, the meta-regressions were performed

Table 1
Pooled SMDs for iCBT versus passive control conditions.

Outcome category	k[a]	SMD[b]	95 % CI	z	p	I^2 (%)[c]
Psychological outcomes						
Depression	23	0.47	[0.36–0.59]	8.02	<0.001	50.10
Anxiety	16	0.34	[0.19–0.48]	4.54	<0.001	53.54
Distress	9	0.43	[0.17–0.69]	3.28	0.001	72.84
Catastrophizing	12	0.43	[0.29–0.58]	5.77	<0.001	30.15
Pain self-efficacy	13	0.40	[0.23–0.58]	4.49	<0.001	69.42
Pain acceptance	7	0.41	[0.26–0.56]	5.39	<0.001	1.61
Physical outcomes						
Pain intensity	24	0.29	[0.16–0.43]	4.17	<0.001	71.87
Fatigue	5	0.26	[0.02–0.49]	2.16	0.031	61.48
Impact on daily life outcomes						
Pain interference	9	0.41	[0.22–0.59]	4.35	<0.001	37.30
Quality of life	12	0.38	[0.22–0.54]	4.58	<0.001	56.19

[a] k = number of studies.
[b] SMD = standardized mean difference.
[c] I^2 = the percentage of total variation between studies due to heterogeneity; an I^2 of 25 % indicates low heterogeneity, an I^2 of 50 % indicates moderate heterogeneity, and an I^2 of 75 % indicates high heterogeneity.

Table 2
Pooled SMDs for iCBT versus active control conditions.

Outcome category	k[a]	SMD[b]	95 % CI	z	p	I^2 (%)[c]
Psychological outcomes						
Depression	9	0.09	[−0.04–0.21]	1.40	0.162	14.91
Anxiety	8	0.08	[−0.03–0.20]	1.44	0.149	0.00
Distress	5	0.40	[0.14–0.66]	3.04	0.002	18.96
Catastrophizing	8	0.09	[−0.09–0.28]	1.02	0.310	36.84
Pain self-efficacy	5	0.06	[−0.13–0.25]	0.65	0.514	23.48
Pain acceptance	5	0.15	[0.01–0.29]	2.09	0.036	0.00
Physical outcomes						
Pain intensity	11	0.12	[−0.01–0.25]	1.87	0.061	26.86
Impact on daily life outcomes						
Pain interference	7	0.16	[−0.10–0.42]	1.19	0.235	67.69

[a] k = number of studies; the references of the studies can be found in Supplemental Digital Content, Appendix G.
[b] SMD = standardized mean difference.
[c] I^2 = the percentage of total variation between studies due to heterogeneity; an I^2 of 25 % indicates low heterogeneity, an I^2 of 50 % indicates moderate heterogeneity, and an I^2 of 75 % indicates high heterogeneity.

again without these high leverage studies. The results of the linear meta-regressions can be found in Table 3 (excluding the high leverage studies), and in Supplemental Digital Content, Table F in Appendix H (including the high leverage studies). The regression plots with and without the two high leverage studies can be found in Supplemental Digital Content, Figs. 22–27 in Appendix H.

The results of the meta-regressions without the two high leverage studies showed that treatment duration (within the range of 4 to 12 weeks) was a significant moderator of the effects on anxiety and quality of life, where each week increase in treatment duration was related to an increase of 0.10 in the effect on anxiety ($p = .03$) and an increase of 0.10 in the effect on quality of life ($p = .046$), compared to the passive control conditions. Moderation by treatment duration was not found for the effects on other outcomes.

Within the iCBT versus active control comparisons, only the outcome of pain intensity was reported in 10 studies and was therefore included in the meta-regression. The results did not show a significant moderation by treatment duration. One study (Gardner et al., 2022) with a treatment duration of 16 weeks (compared to the other studies with a treatment duration ranging from 6 to 12 weeks), was found to have leverage of at least twice the average observed leverage. However, removing this study from the analysis did not affect results in a meaningful way (see Table 3, excluding the high leverage study, and Supplemental Digital Content, Table F in Appendix H, including the high leverage study). The regression plots with and without the high leverage study can be found in Supplemental Digital Content, Fig. 28 in Appendix H.

Subgroup analyses were performed post-hoc to investigate the differences in effect of iCBT interventions where the main mode of therapist contact was synchronous, asynchronous, or a mixture of synchronous and asynchronous. An overview of the main modes of therapist contact, as well as their categorization as either synchronous, asynchronous, or a mixture, is given in Supplemental Digital Content, Table E in Appendix H. For the comparisons of iCBT to passive control conditions, the outcomes of depression (with and without an outlier), catastrophizing, pain self-efficacy, pain acceptance, and pain intensity, had at least three studies in each category of main therapist contact mode and were thus included in the subgroup analyses. Within the iCBT versus active control conditions, no outcome had at least three studies per category of main therapist contact mode and thus subgroup analyses could not be performed. The SMDs per group, per outcome, as well as the results of the subgroup analyses can be found in Table G in Appendix H. The categorical regression plots can be found in Supplemental Digital Content, Figs. 29–34 in Appendix H. The results of the exploratory subgroup analyses showed that effect sizes between groups (i.e., main mode of contact was synchronous, asynchronous, or a mixture) were significantly different for the outcomes of depression ($Q_{between} = 7.40$, $p = .025$) and pain self-efficacy ($Q_{between} = 10.42$, $p = .005$). For depression, the results showed that studies with mixed main modes of contact (SMD = 0.71, $SE = 0.14$) had larger effects of iCBT compared to passive controls than studies with synchronous (SMD = 0.21, $SE = 0.12$, $p < .001$) or asynchronous (SMD = 0.42, $SE = 0.05$, $p = .002$) main modes of contact. However, after removing the outlier from the subgroup analysis of depression, these differences were no longer significant ($Q_{between} = 5.34$, $p = .069$). For pain self-efficacy, the results showed that studies with mixed (SMD = 0.58, $SE = 0.14$) and synchronous (SMD = 0.67, $SE = 0.23$) modes of therapist contact had larger effects of iCBT compared to passive controls, than studies with purely asynchronous main modes of therapist contact (SMD = 0.19, $SE = 0.06$; $p = .029$ and $p = .007$, respectively). The SMDs of studies with mixed or synchronous modes of therapist contact did not differ for pain self-efficacy ($p = .85$). Whether the main mode of contact was synchronous, asynchronous, or a mixture, did not play a moderating role in any of the other outcomes that were included in the subgroup analyses.

3.11. Publication bias

Only outcomes that were assessed in 10 studies or more were included in the publication bias analysis. Therefore, to assess publication bias for iCBT versus passive control conditions, the included outcomes were depression, anxiety, catastrophizing, pain self-efficacy, pain intensity, and quality of life. The funnel plots and statistical tests for asymmetric outcomes can be found in Supplemental Digital Content, Appendix I. Asymmetry was only found in the funnel plot corresponding to the catastrophizing outcome. Egger's test for the catastrophizing outcome confirmed a statistically significant effect (1.12, 95 % CI [0.34, 5.35], $t(10) = 2.53$, $p = .01$). Additionally, Duval and Tweedie's trim and fill analysis showed that five studies were missing from the left side of the funnel plot. After imputing the five missing studies, the adjusted effect size dropped from 0.43 to 0.31, 95 % CI [0.16, 0.46]. No indication of publication bias was found for the other outcomes with any of the

Table 3
Moderation analysis of treatment duration for iCBT versus passive or active control conditions.

Outcome category	k[a]	Treatment duration[b]	*SE*	95 % CI	*z*	*p*
Passive control group						
Psychological outcomes						
Depression[c,d]	21	0.0228	0.04	[−0.06–0.10]	0.56	0.57
Anxiety[c,d]	14	0.0961	0.04	[0.01–0.18]	2.14	0.032
Catastrophizing[c]	11	−0.0188	0.03	[−0.07–0.03]	−0.70	0.48
Pain self-efficacy[c]	12	0.0359	0.06	[−0.08–0.15]	0.60	0.55
Physical outcomes						
Pain intensity[c,d]	22	0.0462	0.03	[−0.02–0.11]	1.34	0.18
Impact on daily life outcomes						
Quality of life[c]	11	0.1004	0.05	[0.0016–0.20]	1.99	0.046
Active control group						
Pain intensity[e]	10	−0.0290	0.04	[−0.11–0.05]	−0.68	0.50

[a] k = number of studies; the references of the studies can be found in Supplemental Digital Content, Appendix G.
[b] Coefficient moderator variable; a positive coefficient corresponds to an increase in effect size relative to the control group per extra week of treatment, whereas a negative coefficient corresponds to a decrease in effect size relative to the control group per extra week of treatment.
[c] High leverage study (Bennell et al., 2018) removed from analysis.
[d] High leverage study (Ferwerda et al., 2017) removed from analysis.
[e] High leverage study (Gardner et al., 2022) removed from analysis.

methods used.

In the iCBT versus active control comparison, only pain intensity was assessed in at least 10 studies (i.e., 11 studies) and therefore included in the publication bias analysis. Egger's test for the pain intensity outcome did not show a statistically significant effect (1.24, 95 % CI [−1.94, 3.66], $t(9) = 0.69$, $p = .25$). However, asymmetry was found in the funnel plot and Duval and Tweedie's trim and fill analysis showed that two studies were missing from the left side of the funnel plot. After imputing the two missing studies, the adjusted effect size dropped slightly from 0.12 to 0.10, 95 % CI [−0.02, 0.22].

4. Discussion

This review provides an up-to-date overview of the efficacy of guided iCBT in chronic pain conditions in 33 studies, including factors that inform an effective and safe delivery. Literature comparing the effect of guided iCBT on psychological, physical and impact on daily life outcomes to passive and active control conditions was reviewed. On average, guided iCBT outperformed passive control conditions for all assessed psychological, physical, and impact on daily life outcomes, with small to medium effects. Guided iCBT was as effective as active control conditions for several psychological outcomes and pain intensity. Furthermore, guided iCBT was more effective than active control conditions for distress with a small to medium effect, for pain acceptance with a small effect, and for pain interference after outlier removal with a small to medium effect. These are promising results, since previous research has shown that pain intensity and physical and mental comorbidities can greatly impact the individual and their social surroundings (e.g., work loss and loss of social contacts) (Dueñas et al., 2016). Moreover, previous research has shown that greater pain intensity, the presence of physical and psychological comorbidities, and a high level of pain interference in daily life are associated with increased healthcare use (Dueñas et al., 2016). Targeting these psychological, physical and impact outcome domains with iCBT may therefore positively affect individuals with chronic pain, their social surroundings, as well as society.

The results from the current meta-analytic review are mostly in line with and expand on results of previous meta-analytic reviews. Any differences between results of the current review and previous reviews could likely be explained by a slightly different and in some cases smaller sample of included studies in previous reviews as compared to the current review. For example, the results on pain intensity are similar to the results of a previous smaller review on guided internet interventions for chronic pain (Martorella et al., 2017) that found small effects for pain in favor of guided internet interventions, when guided internet interventions were compared to passive control conditions. However, in the latter study no significant effects were found for depression or anxiety for the comparison of internet interventions and passive control conditions (Martorella et al., 2017), as opposed to the results in the current meta-analytic review. Besides, the previous review found no differences between guided internet interventions and active control groups for nearly all measures, as opposed to our review, except for a small effect size on pain catastrophizing in favor of guided internet interventions (based on only two studies) (Martorella et al., 2017). Furthermore, the results from the current review are similar to those of another review on guided and unguided internet interventions for patients with chronic pain, including children, for pain interference, pain intensity and catastrophizing when internet interventions were compared to passive control conditions (Buhrman et al., 2016). Our review found slightly higher effects for depression than the previous review for internet interventions versus passive control conditions (medium versus small effect, respectively). Contrary to the results of our review, the latter review found a small to medium effect for disability/interference in favor of active control conditions (based on three studies), when internet interventions were compared to active control conditions (Buhrman et al., 2016). Furthermore, the results of the current review considering the comparison of guided iCBT with passive control conditions are in line with a recent review on guided and unguided iCBT in chronic pain conditions for depression, anxiety, pain intensity, self-efficacy and pain catastrophizing (Gandy et al., 2022). However, the findings differed between the reviews considering the comparison between iCBT and active control conditions. The previous review found small effects for depression, anxiety, disability/interference, and pain catastrophizing in favor of guided and unguided interventions (analyzed as one group) when compared to active control conditions (Gandy et al., 2022). In contrast, the current meta-analysis found significant results for mostly other outcomes when guided iCBT was compared to active control conditions, as discussed above. A partly different and larger sample of studies with active control conditions in our review, an inclusion of different outcomes in the meta-analyses, and a focus on guided iCBT interventions only in our review could have contributed to the different results.

Within this meta-analysis, treatment duration and mode of therapist contact were exploratively researched as moderators of treatment effects. For the iCBT versus passive control conditions, treatment duration (range: 4 to 12 weeks) was a significant moderator of the effects on anxiety and quality of life, where each week increase in treatment duration was related to an increase in the effect on anxiety and quality of

life. Previous research on the effects of treatment duration in iCBT showed mixed results, with some evidence that a longer treatment duration (>6 weeks or ≥6 modules) produced larger effects on depression than a shorter treatment duration (≤6 weeks or <6 modules) when iCBT was compared to different control groups (van Beugen et al., 2014; Păsărelu et al., 2017). However, in the current review, two studies with an extra-long treatment duration (i.e., 24 and 26.07 weeks), that were removed in sensitivity analyses, appeared to consistently decrease and often reverse the regression coefficient from positive to negative. This could potentially imply that studies with a very long duration are associated with decreased effect sizes for every extra week of treatment, compared to shorter treatments. Nevertheless, since only two studies had a very long treatment duration, more research is needed to draw conclusions on the ideal treatment duration for iCBT in chronic pain. Future research could compare guided iCBT in groups with a different treatment duration (e.g., a group with a short treatment duration, a medium duration, and a long duration) to further investigate the impact of this variable.

In a different exploratory moderator analysis on main mode of therapist contact, it was shown that main mode of contact (synchronous, asynchronous or a mix of both) was not related to differences in effect sizes in most outcomes. However, studies with mixed and synchronous main modes of therapist contact had higher effects on pain self-efficacy than studies with purely asynchronous main modes of contact. To our knowledge, this is the first meta-analysis on iCBT in chronic pain that investigated this moderator. It should be noted that subgroup analyses are always observational (Higgins and Green, 2011), and the current subgroup analyses were performed post-hoc. More research is needed to draw firm conclusions on the most appropriate mode of contact for different outcomes to inform optimal use of it in clinical practice. For example, in an RCT on iCBT for chronic pain, patients could be allocated to a group with synchronous therapist-patient contact, a group with asynchronous contact, and a group with a mix of both modes of contact to investigate potential differences in efficacy of contact modes. Due to inconsistent reports on therapist guidance within the included studies in the present review, the amount of therapist involvement could not be researched as a moderator. Although therapist-guided iCBT appears to be beneficial as shown by the intervention effects in the current review, therapist involvement (e.g., total therapist time spent, quality of the therapeutic relationship) needs to be more clearly and consistently reported on in order to make specific recommendations for clinical practice.

To our knowledge, this is the first review on guided iCBT in chronic pain to systematically report on several IMMPACT-recommended outcome domains related to participant experience and the safety of the treatment, namely: (1) participant ratings of global improvement and treatment satisfaction, (2) the extent of and reasons for dropout as part of the participant disposition domain, and (3) adverse events and symptoms (or negative treatment effects) (Turk et al., 2003; Dworkin et al., 2005). Within the studies in this review addressing these outcome domains, satisfaction with treatment was generally high, and approximately half of the participants experienced much or very much improvement compared to before treatment. The discrepancy between the high satisfaction ratings and the medium ratings of improvement could indicate that ratings of global improvement measured by a single item, as was done in several studies, may not be an adequate reflection of participants' perception of important change (Turk et al., 2003). An alternative to single-item measures of global improvement could be multiple-item measures of improvement that assess improvement in different domains and include priorities for improvement of participants (e.g., see Cardol et al., 2021). Furthermore, dropout was substantial and is a common issue in internet-based treatments (Ryan et al., 2018). Technical difficulties or lack of computer skills were often mentioned as dropout reasons. A more extensive training in using the internet program for patients and offering proactive technical support may reduce attrition. Besides, usability of iCBT for patients with poor computer skills could be further researched and potentially improved upon and effects on dropout could be assessed. Next, reported adverse events were found to be minor and temporary in some studies, whereas in other studies no such information was provided. In none of the studies serious adverse events were reported, although some of the mentioned reasons for dropout could be classified as serious adverse events (e.g., hospitalization) and were not reported as such. There was a considerably higher prevalence of adverse events in the intervention group than in the control group in two cases (Hedman-Lagerlöf et al., 2018; Bennell et al., 2017). In both cases, the most commonly reported adverse event was increased pain, which might be related to the inclusion of physical exercises or exposure exercises in the treatments. Combined with the small proportion of participants showing deterioration on certain outcome measures, iCBT interventions have the potential to be safe for participants, but the evidence so far is too limited to draw definite conclusions. Unfortunately, comparing studies by meta-analysis was not feasible for the IMMPACT measures summarized above, due to the limited number of studies providing data and inconsistent assessment and reporting. A more common assessment of the recommended outcome domains, as well as more consistency in definition and assessment of adverse events and negative treatment effects (e.g., by utilizing previously reported definitions and recommendations; Rozental et al., 2014) in future research on internet-based interventions for chronic pain could foster comparison by meta-analysis and facilitate evaluations of interventions on the basis of their benefits as well as their risks (Turk et al., 2003; Dworkin et al., 2005).

5. Limitations

Some limitations of this meta-analysis and the included studies should be mentioned. Within this meta-analysis, the heterogeneity in content of the iCBT interventions, types of active control conditions, and measurement scales used may complicate the interpretation of pooled effects. Besides, publication bias was found for the catastrophizing outcome, when iCBT was compared to passive control conditions. A correction for missing studies resulted in a lower adjusted effect size for this outcome. Publication bias could not be precluded for several outcomes in studies that compared iCBT to an active control condition, since it could only be assessed for one outcome, due to a lack of studies. Regarding limitations of the included studies, guided iCBT was often performed in patients with different chronic pain conditions merged together in the included studies, which impeded subgroup analyses of the effects of iCBT per chronic pain condition in this meta-analysis. Furthermore, this also implied that pain conditions with a potentially different pain intensity and pain frequency (such as headache [Andersson et al., 2003; Devineni and Blanchard, 2005] vs. fibromyalgia [e.g., Simister et al., 2018; Vallejo et al., 2015]) were analyzed as one group in this meta-analysis, which could be viewed as a strength (providing overarching results of iCBT in chronic pain) as well as a limitation. Furthermore, follow-up measurements were not uniformly applied and reported on across studies, which precluded aggregating results. Also, interventions in the individual studies were often scarcely described, which hindered any content analyses providing specific indications of what works and what needs to be improved within these interventions. Finally, all studies but two included an unclear risk of bias and/or a high risk of bias of some form, which may affect the interpretation and generalization of results. An unclear risk of bias was due to limited descriptions, which could be prevented by following RCT reporting guidelines (Eysenbach and Consort-Ehealth Group, 2011). Besides, blinding of outcome assessment, which was assessed as a risk of bias domain in this review, is commonly difficult to fully achieve in iCBT trials, since patients are usually aware of the received intervention and patient-reported measures would thus be collected in knowledge of the received intervention. Therefore, blinding of clinician-rated outcomes and blinding of the statistician were evaluated in this review. Whilst blinding of clinician-rated outcomes was usually successfully

implemented in the included studies, blinding of the statistician was most often not described. Future studies should describe in more detail any blinding procedures in data analysis to promote risk of bias analysis in this domain.

6. Future directions

Regarding further future directions, more studies including between-group long-term follow-up are needed. To limit its scope, cost-effectiveness analyses were not included in this review, nor were these analyses often performed within the included studies. Studies on cost-effectiveness are important to assess the feasibility of iCBT implementation in practice and should be included in future research. Besides, certain potential moderators of treatment effect (e.g., patient characteristics, such as age, sex, education level, baseline levels of distress) were not researched in this review to limit its scope. Future research should research these subgroups in order to make specific recommendations for clinical application of (guided) iCBTs. Regarding the design of RCTs, current practice is usually to assess a treatment package as a whole using an RCT and to then ask questions about why something worked, or not, using post-hoc analyses that are subject to bias due to a lack of random assignment (Collins et al., 2005). If the goal is to progressively optimize interventions, the identification of active ingredients within an intervention should be a primary consideration in the design of an experiment. Methods that are specifically designed for this goal already exist and include the multiphase optimization strategy (MOST) and sequential multiple assignment randomized trials (SMART; Collins et al., 2007). These methods can be used to examine the effectiveness of individual components, their interactions, and the optimal dosage of each component through randomized experimental design (including, for example, treatment duration and involvement of a therapist). Next, for meta-analytic purposes and to formulate recommendations for clinical practice, intervention components, therapist guidance, and factors related to participant experience and the safety of the treatment (e.g., IMMPACT factors of adverse events, improvement and treatment satisfaction, and dropout) should be described more consistently and in more detail in future research.

7. Conclusions

ICBT could be an important addition to the treatment of chronic pain, impacting psychological, physical, and pain impact on daily life outcomes. Patients are overall satisfied with treatment and indications are the treatment is safe in terms of reported adverse events. However, more consistent reporting on participant experience and safety factors is needed to draw definitive conclusions. The next step is to optimize this intervention through a better understanding of its individual components and their interactions. Moreover, a focus on usability, cost-effectiveness analyses, and long-term follow-up analyses can clarify the efficacy and feasibility of iCBT for chronic pain in clinical practice.

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Declaration of competing interest

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Appendix A. Supplementary data

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