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STATE OF THE ART REVIEW

New generation psychological treatments in chronic pain

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ABSTRACT

Chronic pain conditions are common and have a considerable impact on health and wellbeing. This impact can be reduced by cognitive behavioral therapy (CBT), the most commonly applied psychological approach to chronic pain. At the same time, CBT continues to develop, and now includes what is sometimes called "third wave" CBT. In this review, we examine the evidence for application of acceptance and commitment therapy (ACT), a principal example of this new wave or latest generation of treatment approaches, in people with chronic pain. We identified 25 randomized controlled trials of ACT for adults with chronic pain. Across the included trials, small to large effect sizes favoring ACT were reported for key outcomes including pain interference, disability, depression, and quality of life. Evidence from three studies provided some support for the cost effectiveness of ACT for chronic pain. Evidence also supported the mediating role of theoretically consistent processes of change (psychological flexibility) in relation to treatment outcomes. Investigation of moderators and predictors of outcomes was limited and inconsistent. In future, a greater focus on process based treatments is recommended. This should include continued identification of evidence based processes of change, and research methods more suited to understanding the experience and needs of individual people.

Introduction

Chronic pain is conventionally regarded as pain that persists or recurs past normal healing time, typically three months. The condition has always been challenging to manage in conventional healthcare. Classifying chronic pain has been difficult, leading to confusion and possible neglect in research and treatment pathways.[1] To remedy this, chronic pain has been categorized as primary or secondary: primary when it is the main or only complaint and a disease in its own right, and secondary when pain is a symptom of an underlying disease.[1] In this scheme, a defining feature of chronic primary pain, in addition to being persistent, is that it is associated with significant emotional distress and interference with daily functioning that cannot be accounted for by another condition.[2] This classification clearly defines chronic primary pain as a condition in its own right. It formally recognizes chronic pain as a legitimate focus of clinical concern, whether it is the main concern or accounted for by another condition.

Chronic pain is often described as a bio-psycho-social problem.[3] Although this description does not provide a specific model or mechanism of pathology, it is a reminder to consider factors from these three domains as potentially influencing the development of chronic pain conditions, or as targets of intervention. Similarly, it is customary to define pain outcomes broadly, including not just pain intensity but also interference with activity, emotional functioning, and social role functioning, and to include satisfaction with treatment and global impression of change.[4] Even within pain itself, the intensity is known to be determined by cognitive, emotional, and social factors, shaping what we feel, what it means, and how we immediately respond to what we feel.[5] In fact, all the ways we respond in the context of chronic pain, in every aspect of our lives, are shaped by our learning history.[5][6] Studies of outcomes in chronic pain show that psychosocial factors are better indicators than pain intensity when accounting for variance in key outcomes in emotional, physical, and social functioning, work, or use of healthcare.[7][8]

The purpose of this review is to provide an updated, comprehensive, and inclusive summary of evidence for acceptance and commitment therapy (ACT), a recent development in cognitive behavioral therapy (CBT), in treatment of chronic pain, including headache. Our review includes long term outcomes, cost effectiveness, mechanisms of change, and moderators or predictors of outcome. The target audience includes primary care and hospital based physicians, nurses, physiotherapists, psychologists, or other healthcare providers with or without specialist experience in forms of CBT for chronic pain.

Sources and selection criteria

One of the authors (LY) conducted an electronic search in PsycInfo, Medline, and CINAHL to identify articles reporting randomized controlled trials (RCTs) of ACT for chronic pain. The search strategy was adapted from existing systematic reviews of ACT for chronic pain.[9][10] Appendix A (see supplementary files) describes the search strategy in full. Initially, we identified 716 articles. The earliest RCT of ACT for chronic pain we identified in existing systematic reviews was published in early 2000, therefore we limited the search results to English language articles published between 2000 and 2021. This process eliminated 29 articles. After duplicates were excluded, 407 articles remained. We then screened these articles based on their titles, which eliminated 229. Next, we reviewed 178 abstracts to further exclude irrelevant articles, which eliminated 122. Finally, two authors (LY, LM) independently read 56 full texts to identify relevant articles. We included only articles that were written in English language, had RCT designs, had adult participants with chronic pain, had participants

treated with ACT, contextual CBT, or "acceptance-based" therapy, those which clearly focused on increasing aspects of psychological flexibility; and those which included one or more of the following outcomes: pain, pain interference, disability, depression, anxiety, or quality of life. When two authors did not agree on the inclusion of an article, it was discussed until a consensus was agreed. Through this process, we identified 24 articles and included them in the current review. To ensure comprehensiveness of the literature search, we also reviewed existing systematic reviews of RCTs of ACT for chronic pain, as well as the reference lists of included articles to identify potential articles. Through this process, one additional article was identified and included in the current review, leading to a total of 25 articles included (full reference set included at the end of the article). Figure 1 depicts the search and selection process. The data summarized here were extracted by two authors (LY, KV) and checked by the third (LM).
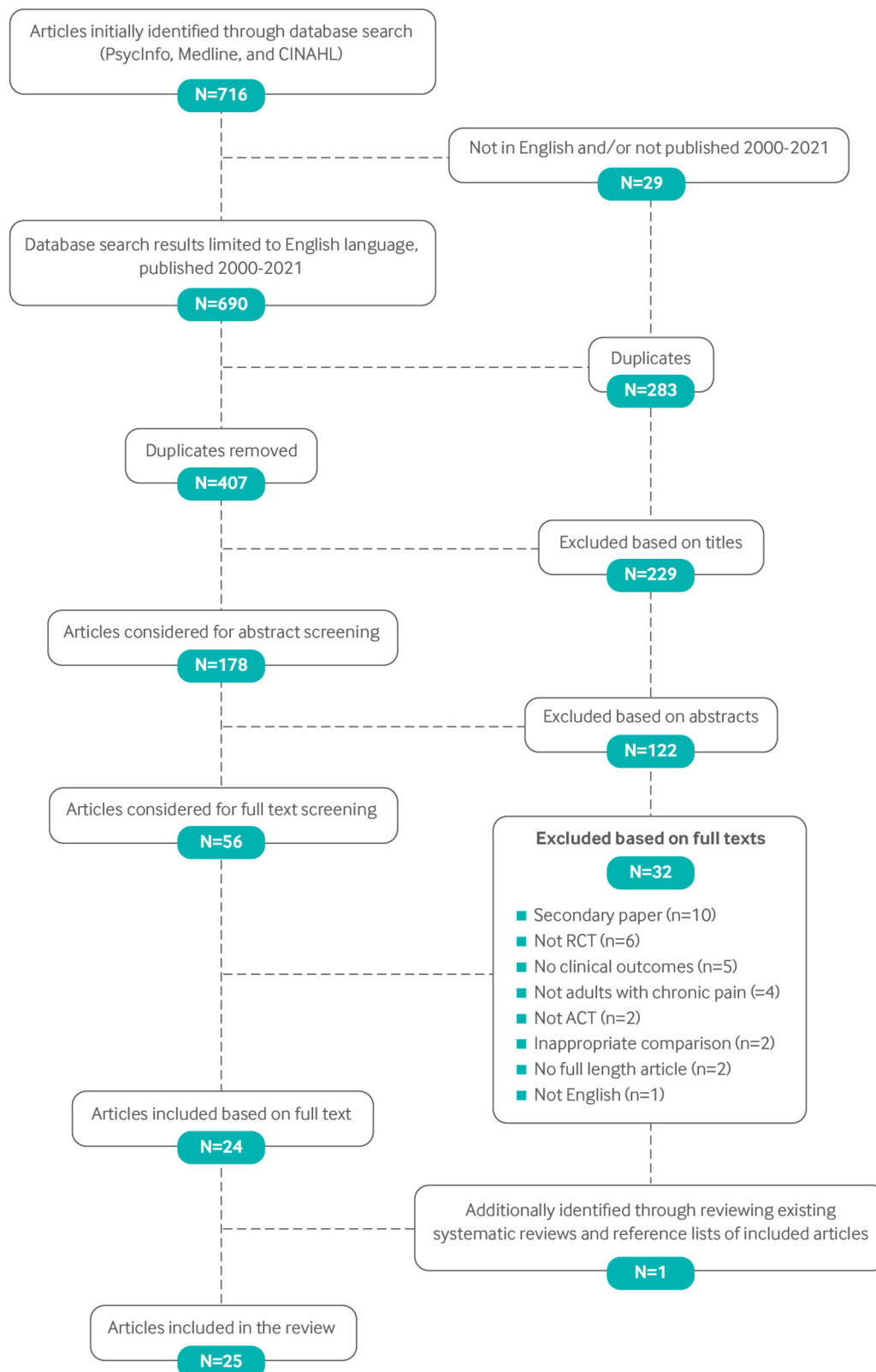
Fig 1 | Flowchart of article screening and selection process

Prevalence and impact of chronic pain

Chronic pain conditions are common. Population based prevalence estimates vary between 10% and 50% of adults, depending on methods used,[11 12] with more reliable estimates around 20%.[11 13] Chronic pain is more prevalent in women, and is associated with advancing age, socioeconomic deprivation, unemployment, smoking, comorbid chronic physical and mental health conditions,

insomnia, and obesity.[12] Chronic pain is particularly associated with poor mental health, including depression and anxiety disorders,[12 13] and an increased risk of suicide.[14]

The impact of chronic pain is considerable, particularly in people with moderate to severe pain. This group of patients is often unable to carry out simple, daily, physical tasks or to exercise; they lose contact with family and friends, are unable to sleep adequately, and either lose jobs or need to change jobs.[13 15] "Disability weights" refers to health loss associated with a condition, and "years lived with disability" (YLD) represents the statistical summary that is the product of the prevalence of a condition multiplied by the disability weight. In the Global Burden of Disease Study 2017, low back pain, just one type of pain condition that is typically chronic or recurrent, was identified as the leading global cause of YLD.[16] YLD caused by back pain peaks in people of working age and increases over time, meaning this burden is particularly costly and urgently needs solutions. Another persistent pain condition, headache, is the third highest cause of YLD in people aged 10 to 24 and the seventh highest in those aged 25 to 49, based on a total of 369 diseases.[17] "Health utility" is a global measure of quality of life that combines a person's health state with their preference for that health state. A recent, large, community based study of health utility in Canada (n=12 146 matched pairs, with or without pain) showed that people with chronic pain reported lower quality of life than most other chronic diseases, including heart disease, diabetes, and chronic obstructive pulmonary disease.[18]

Generations of cognitive and behavioral treatment

CBT, the most common psychological approach to treating chronic pain,[19] is a broad family of specific therapy types. These range widely in structure and format of delivery, and include many varied methods, typically delivered to people with chronic pain as standardized packages of multiple methods. These methods traditionally included training in relaxation, goal setting, methods to challenge negative thoughts, and other approaches to manage stress or to improve daily activity. Newer treatment packages often incorporate some of these same methods but also include exposure therapy, mindfulness, and methods to enhance acceptance or psychological flexibility.

CBT is often regarded as having developed in three generations or "waves." The first two waves reflect a dominant focus on either behavior therapy or cognitive therapy, while the "third wave" is a little more difficult to characterize.[20] Easier to describe are the specific forms of therapy included in the third wave: ACT, mindfulness based therapies, dialectical behavior therapy, behavioral activation therapy, and functional analytic psychotherapy, among others.[21] Within chronic pain treatment, CBT has more or less followed these same three waves, with the first two typically called operant behavioral[22] and cognitive behavioral.[23] The term "third wave" may be used less frequently in relation to chronic pain treatments specifically, but developments in psychological treatments for chronic pain clearly mirror the new generation of developments in the wider field of CBT. These developments in psychological treatments for chronic pain are dominated by two types: mindfulness based therapies and ACT.[9] In the past, studies of mindfulness based treatments and ACT for chronic pain were often reviewed together as related approaches,[9] but this is no longer necessary or desirable, as enough studies of both are now available to review in their own right, and distinctions in philosophy, methods, and therapeutic processes can be seen between the two approaches that merit separate attention.

ACT is essentially a form of CBT that focuses on enhancing psychological flexibility as a process of change to produce outcomes.[24] Psychological flexibility is a combination of acceptance, awareness, and behavior change processes. It is the ability to be clear in, guided by, and persistent in taking action toward one's goals and values, and aware of or sensitive to situations as they occur, without unproductive resistance or being dominated by feelings or thoughts.[25 26] The psychological flexibility model has six inter-related processes or facets that can be represented as continuums ranging from inflexible to flexible, can be targeted separately, and combine to form the one unifying whole. These are further presented in figure 2.
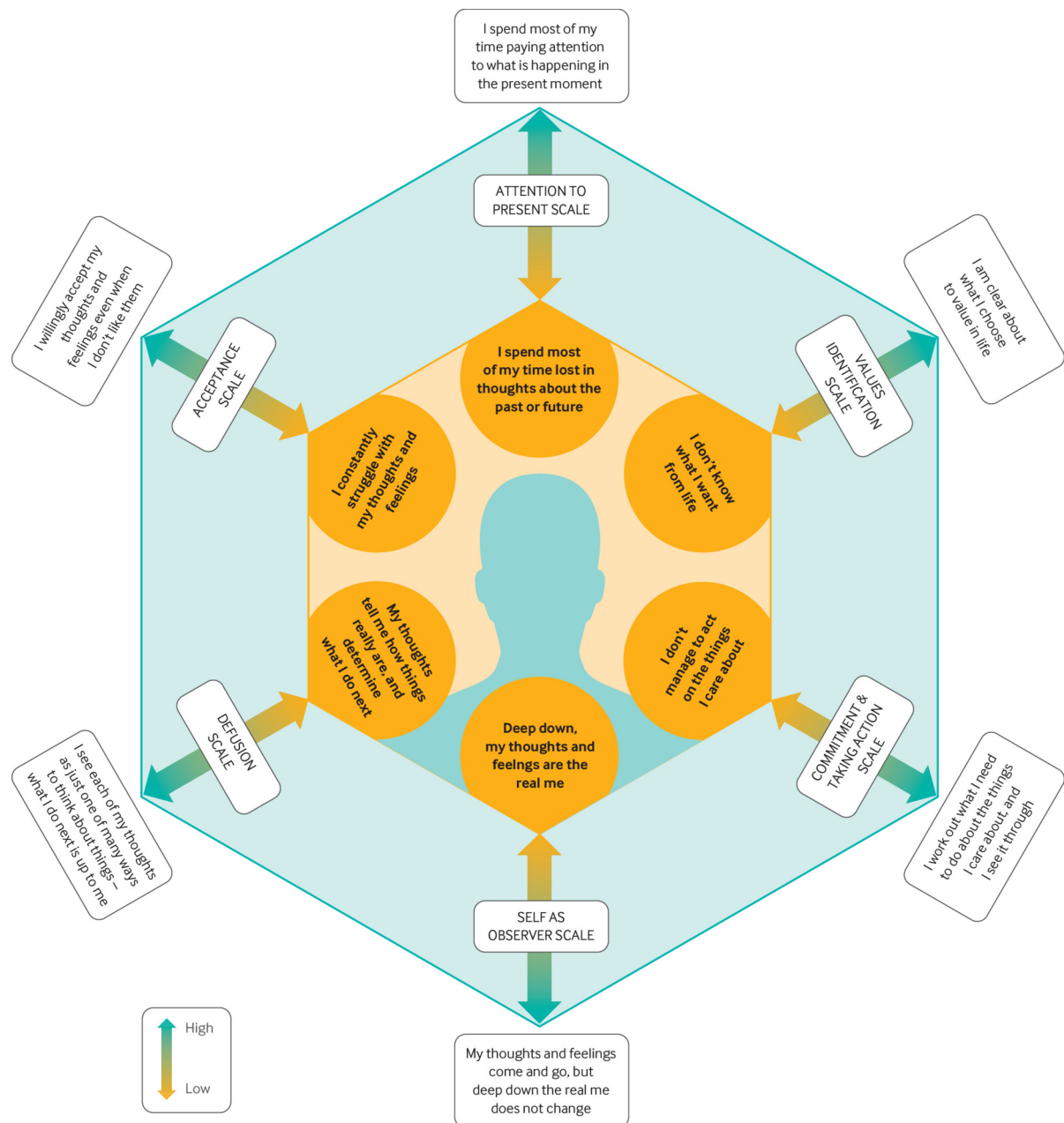
Fig 2 | The psychological flexibility model, the therapeutic focus of ACT

Evidence for ACT in chronic pain is emerging at an increasing rate, and includes at least seven RCTs since 2020. An updated and comprehensive summary specifically with respect to controlled comparison studies is needed. The most recent systematic review of ACT for chronic pain, a Cochrane review, was highly selective and included only a minority of the trials currently available.[19] The most recent more inclusive systematic review was published in 2016[10] and, again, this needs updating. In addition, some reviews

exclude studies of headache[27] but this is unnecessary, particularly when results are not being meta-analyzed. Relevant studies of ACT for headache have not yet been reviewed within the wider range of conditions.

Characteristics of treatment studies

The 25 trials summarized here included 2505 adult participants. Fifteen of the 25 trials recruited participants with mixed musculoskeletal pain conditions; three focused on fibromyalgia, three on headache, and one each on low back pain, painful diabetic neuropathy, and whiplash associated disorder. The treatments were most frequently group based (14 trials), followed by internet based (six trials), individual face to face (three trials), telephone based (two trials), and one was based on self-help guided by a workbook. Twenty one trials featured two-arm designs, and four included three arms. The most common comparison arm was treatment as usual (eight trials); seven included wait list controls, four included support or education, three included relaxation, two each included medication and physiotherapy, and one included unguided online treatment, expressive writing, and CBT. Study details are included in table 1.

Table 1 | Characteristics of included studies

Author (year)	Sample and setting		Treatment	Comparator(s)	Assessment points (sample size)
	Pain population	Setting/country			
Dahl J, et al (2004)[28]	Public health service employees with chronic stress and pain	Work site or at home/Sweden	ACT+TAU, 4×1 hour individual weekly sessions	TAU	Randomized at baseline: n=19 Post-treatment and follow-up: unclear
Wicksell, et al (2008)[29]	Adults with chronic pain and whiplash associated disorders	Outpatient clinic/ Sweden	ACT, including 10 individual sessions over 8 weeks. Eight sessions with clinical psychologist, 2 with physician	Wait list	Randomized at baseline: n=22 4 month follow-up: n=10
Thorsell J, et al (2011)[30]	Adult with chronic pain	Specialty university pain clinic/Sweden	ACT, including self-help book (*Living Beyond Your Pain*) and CD + weekly therapist telephone support	Applied relaxation, including self-help manual and CD	Randomized at baseline: n=115 Post-treatment (8 weeks): n=55 6 month follow-up: n=53 12 month follow-up: n=32
Wetherell, et al (2011)[31]	Adults with chronic non-cancer pain	Primary care and community/US	ACT, including 8 weekly 1.5 hour group treatment sessions from clinical psychologists	Cognitive behavior therapy, including 8 weekly 1.5 hour treatment sessions from clinical psychologists	Randomized at baseline: n=114 6 month follow-up: n=99
Mo'tamedi, et al (2012)[32]	Women outpatients with chronic headache	Specialty clinic for headache/Iran	ACT+TAU, 8×90 minute weekly group sessions	TAU	Randomized at baseline: n=30 Post-treatment: n=26
Wicksell, et al (2013)[33]	Adult women with fibromyalgia	Outpatient clinic/Sweden	ACT, including 12 weekly 1.5 hour sessions, 10 group sessions delivered by clinical psychologists, 2 sessions delivered by physicians	Wait list	Randomized at baseline: n=43 Post-treatment: n=36 3-4 month follow-up: 33
Buhrman, et al (2013)[27]	Adults with chronic pain	Specialty university pain center/Sweden	ACT, internet delivered, including 7 "sections," about one section per week guided by students in clinical psychology	Moderated weekly online discussion forum (topics on pain)	Randomized at baseline: n=76 Post-treatment: n=61 6 month follow-up: n=29* *only ACT
McCracken, et al (2013)[34]	Adults with chronic pain	General practice/UK	Brief group ACT, 4×4 hour group sessions delivered over 2 weeks by clinical psychologists	TAU	Randomized at baseline: n=73 Post-treatment: n=58 3 month follow-up: n=56
Luciano, et al (2014)[35]	Adults with fibromyalgia (96.2% women)	Primary healthcare centers/Spain	GACT, including 8×2.5 hour sessions	RPT, wait list	Randomized at baseline: n=156 Post-treatment: n=142 6 month follow-up: n=136
Kemani, et al (2015)[36]	Adults with longstanding pain	University behavioral medicine unit/Sweden	ACT, including 12 weekly 90 minute group sessions	Applied relaxation including 12 weekly sessions (90 minutes)	Randomized at baseline: n=60 Post-treatment: n=43 3 month follow-up: n=42 6 month follow-up: n=37
Pincus, et al (2015)[37]	Adults with low back pain and high psychological risk	Musculoskeletal physiotherapy services/UK	CCBT (ACT), including up to 8×50 minute individual sessions	Physiotherapy	Randomized at baseline: n=89 3 month follow-up: n=67 6 month follow-up: n=54
Trompetter, et al (2015)[38]	Adults with chronic pain	Community/Netherlands	ACT, internet delivered, guided self-help intervention (9-12 weeks)	Internet based expressive writing, wait list	Randomized at baseline: n=238 Post-treatment: n=172 6 month follow-up: n=167
Alonso-Fernández, et al (2016)[39]	Older adults with chronic musculoskeletal pain living in nursing home	Nursing homes/Spain	ACT combined + selective optimization with compensation training, including 9×120 minute weekly group sessions	Minimal support group including a 2 hour pain education session	Randomized at baseline: n=101 Post-treatment: n=53
Lin, et al (2017)[40]	Adults with chronic pain	Community/Germany	ACT, online treatment (ACTonPain) with guidance from psychologist, including an introduction and 7 modules, delivered weekly	ACTonPain without guidance, wait list	Randomized at baseline: n=302 Post-treatment: n=128 6 month follow-up: n=84
Hara, et al (2018)[41]	Adults on long term sick leave with chronic pain disorders, chronic fatigue, or common mental health disorders	Occupational rehabilitation center/Norway	ACT consistent follow-up, after occupational rehabilitation, delivered via telephone, monthly for 6 months + standard community based follow-up	Standard community based follow-up	Randomized at baseline: n=213 1 year follow-up: n=208

Table 1 | Characteristics of included studies *(Continued)*

Author (year)	Sample and setting		Treatment	Comparator(s)	Assessment points (sample size)
	Pain population	Setting/country			
Scott, et al (2018)[42]	Adults with complex chronic pain	Specialty interdisciplinary pain center/UK	ACT, ACT including 8 online sessions, done over 5 weeks	TAU	Randomized at baseline: n=63 3 month follow-up: n=48 9 month follow-up: 49
Simister, et al (2018)[43]	Adults with fibromyalgia	Clinic and community/Canada	ACT, online including 7 modules during 2 months, 1 module per week, plus TAU	TAU	Randomized at baseline: n=67 Post-treatment (8 weeks): n=58 3 month follow-up: n=50
Wiklund, et al (2018)[44]	Adults with chronic neck, low back, or generalized pain	University pain center/Sweden	ACT based stress management, including 7 weekly 2 hour group based sessions during 7 weeks	Physical exercise in groups for 1 hour twice a week plus home exercise for 8 weeks. Moderated group discussions related to pain 2 hours weekly for 7 weeks	Randomized at baseline: n=299 Post-treatment: n=200 6 month follow-up: n=175 12 month follow-up: n=168
Dindo, Recober, et al (2020)[45]	Adults with depression and migraine	Hospitals, clinics, and community/US	1 day ACT group workshop + migraine education (ACT-ED): 5-6 hours	Active support plus migraine education workshop (S-ED): 5-6 hours	Randomized at baseline: n=136 3 month follow-up: n=96 6 month follow-up: n=91
Dindo, Johnson, et al (2020)[46]	Adult military veterans with mild brain injury, distress, and chronic pain	Veterans Health Administration medical center/US	1 day ACT group workshop + education, about 5 hours	TAU	Randomized at baseline: n=39 (2:1 randomization) 3 month follow-up: n=30
Taheri, et al (2020)[47]	Adults with painful diabetic neuropathy	Psychiatry clinic/Iran	8 outpatient ACT group sessions, 1 per week, plus medication for neuropathic pain	Medication for neuropathic pain	Randomized at baseline: n=50 Post-treatment (8 weeks): n=41 3 month follow-up: n=41
Vasiliou, et al (2020)[48]	Adults with primary headache disorders	Neurology clinics and community/Cyprus	ACT, in groups including 8 weekly 1.5 hour treatment sessions from clinical psychology trainees	Wait list	Randomized at baseline: n=94 Post-treatment: n=61 3 month follow-up: n=62
Vowles, et al (2020)[49]	Adult military veterans with chronic pain and opioid misuse	Veterans affairs medical center/US	ACT + mindfulness based relapse prevention, 12 weekly 1.5 hour group sessions from clinical psychologists, plus specialist medical care for co-occurring chronic pain and opioid misuse	Specialist medical care for co-occurring chronic pain and opioid misuse	Randomized at baseline: n=35 6 month follow-up: n=22
Roslyakova, et al (2020)[50]	Adults with chronic pain	Specialist university chronic pain center/France	ACT, 8×2 hour weekly group sessions + group psychoeducational relaxation therapy, 7 weekly group sessions of 1.5 hours	Psychoeducational relaxation therapy alone	Randomized at baseline: 138 Consent to participate: 94 Post-treatment: 88 3 month follow-up: unclear
Rickardsson, et al (2021)[51]	Adults with chronic pain	Community/Sweden	ACT (iACT), guided online, structured in a "microlearning" format, short learning interactions with practical/experiential exposure, every weekday for 8 weeks	Wait list	Randomized at baseline: n=113 Post-treatment: n=100 3 month follow-up: n=43* 6 month follow-up: n=38* 12 month follow-up: n=37* *only ACT

ACT ED= ACT plus education; CCBT=Contextual CBT; GACT=group acceptance and commitment therapy; iACT=Internet based ACT; TAU=treatment as usual; RPT=recommended pharmacological treatment; S-ED=social support plus education.

Summary of evidence for outcomes

In trials of treatments for chronic pain, consensus guidance recommends including clinical outcome measures in domains such as pain, physical functioning, and emotional functioning, as well as role functioning and coping, when possible.[4] Measures of pain, pain interference, disability, depression, anxiety, and quality of life appear frequently in the studies we reviewed, and we selected these to summarize the results. Summary effect size results are included in table 2. From the 25 trials, 23 reported effect sizes or allowed their calculation from reported results. From these 23 trials, 95 effect sizes

were obtained based on all comparisons reported that involved ACT. In selecting effect sizes for summary, the focus was on immediate post-treatment effects, although follow-up effect sizes also appear in table 2. When a choice of calculated effect sizes appeared in studies, those based on intention to treat analyses were chosen over per protocol. In some cases, multiple measures of the same variables were present within the same trial, meaning there were more tests of an effect than there were trials. All of these were included to provide a complete accounting of the data available. A limitation is that not every effect is completely independent.

Table 2 | Summary of selected effects of comparisons, including ACT versus other comparison conditions or controls

Author (year)	Effect sizes	
	Outcomes	Psychological flexibility processes
Dahl, et al (2004)[28]	$\eta^2 p$ Overall Quality of life: ns Pain: ns	None
Wicksell, et al (2008)[29]	$\eta^2 p$ Overall Pain disability: 0.44 Satisfaction with life: 0.40 Anxiety: 0.16 Depression: 0.60 Pain intensity: 0.01 Pain interference: 0.31	$\eta^2 p$ Overall Psych inflexibility—avoidance: 0.61 Psych inflexibility—cognitive fusion: 0.34
Thorsell, et al (2011)[30]	Cohen's d Overall Satisfaction with life scale: 0.31 Depression: 0.22 Anxiety: 0.20 Level of function (pain interference): 0.39 Pain intensity: 0.35	Cohen's d Overall Pain acceptance: 0.42
Wetherell, et al (2011)[31]	Cohen's d Post-treatment; 6 month follow-up Pain interference: 0.00; 0.13 Pain intensity: 0.00; 0.06 Depression: 0.07; 0.07 Pain anxiety: −0.13; −0.12	Cohen's d Post-treatment; 6 month follow-up Pain acceptance: 0.17; 0.06
Mo'tamedi, et al (2012)[32]	Cohen's d Post-treatment Pain intensity-sensory: ns Disability: 0.93 Anxiety: 2.54	None
Buhrman, et al (2013)[27]	Cohen's d Post-treatment Anxiety: 0.18 Depression: 0.44 Quality of life: ns Pain interference: 0.56 Pain severity: ns	Cohen's d Post-treatment Pain acceptance:-activity engagement: d=0.60 Pain acceptance-pain willingness: d=0.49 CPAQ-total: d=0.41
McCracken, et al (2013)[34]	Cohen's d Post-treatment; 3 month follow-up Disability: 0.32; 0.59 Depression: 0.46; 0.58 Pain: 0.44; 0.32 ITT post-treatment; 3 month follow-up Disability: 0.36; 0.37 Depression: 0.46; ns Pain: ns; ns Treatment completer post-treatment; 3 month follow-up Disability: 0.45; 0.55 Depression: 0.53; 0.59 Pain: ns; ns	Cohen's d Post-treatment; 3 month follow-up Pain acceptance: 0.26; 0.64 General psychological acceptance: 0.20; 0.22 ITT post-treatment; 3 month follow-up Pain acceptance: 0.23; ns General psychological acceptance: ns; ns Treatment completer post-treatment; 3 month follow-up Pain acceptance: 0.51; 0.59 General psychological acceptance: ns; ns
Wicksell, et al (2013)[33]	Cohen's d Post-treatment; 3-4 month follow-up Pain disability: 0.75; 0.73 Fibromyalgia impact: 0.41; 0.66 Mental quality of life: 0.84; 1.06 Depression: 0.44; 0.64 State anxiety: 0.51; 0.55 Pain intensity: 0.38; 0.82	Cohen's d Post-treatment; 3-4 month follow-up Psychological inflexibility: 1.06; 0.72

Table 2 | Summary of selected effects of comparisons, including ACT versus other comparison conditions or controls *(Continued)*

Author (year)	Effect sizes	
	Outcomes	Psychological flexibility processes
Luciano, et al (2014)[35]	Cohen's *d* Post-treatment; 6 month follow-up GACT *v* RPT Fibromyalgia impact: 1.43; 1.43 Pain: 0.62; 0.47 Quality of life: 0.85; 0.66 Depression: 0.43; 0.37 Anxiety: 0.36; 0.39 Post-treatment; 6 month follow-up GACT *v* wait list Fibromyalgia impact: 2.35; 2.11 Pain: 0.93; 0.80 Quality of life: 1.06; 0.84 Depression: 1.01; 0.88 Anxiety: 0.77; 0.85	Cohen's *d* Post-treatment; 6 month follow-up GACT *v* RPT Pain acceptance: 1.05; 1.01 Post-treatment; 6 month follow-up GACT *v* wait list Pain acceptance: 1.21; 1.14
Kemani, et al (2015)[36]	Cohen's *d* Post-treatment Pain disability: 0.61 Pain: ns Mental quality of life: 0.50 Anxiety: ns Depression: 0.35	Cohen's *d* Post-treatment Pain acceptance: 0.90
Pincus, et al (2015)[37]	Effect sizes unavailable	
Trompetter, et al (2015)[38]	Cohen's *d* Post-treatment; 3 month follow-up ACT *v* expressive writing Pain interference: 0.33; 0.47 Depression: ns; 0.49 Anxiety: ns; ns Pain intensity: 0.23; 0.38 Pain disability: ns; 0.40 Post-treatment; 3 month follow-up ACT *v* wait list Pain interference: ns; ns Depression: ns; 0.38 Anxiety: ns; ns Pain intensity: ns; 0.28 Pain disability: ns; ns	Cohen's *d* Post-treatment; 3 month follow-up ACT *v* expressive writing Psychological inflexibility: 0.40; 0.47 Mindfulness: ns; ns Engaged living: ns; ns Post-treatment; 3 month follow-up ACT *v* waitlist Psychological inflexibility: 0.60; 0.54 Mindfulness: ns; 0.36 Engaged living: ns; ns
Alonso-Fernández, et al (2016)[39]	ηp2 Post-treatment Pain: ns Depression: 0.03 Pain anxiety: 0.07	ηp2 Post-treatment Pain acceptance: 0.09
Lin, et al (2017)[40]	Cohen's *d* (ITT) Post-treatment; follow-up Guided ACT *v* WL Pain interference: 0.58; 0.58 Depression: ns; ns Anxiety: ns; ns Pain intensity: ns; ns Unguided ACT *v* WL Pain interference (MPI): ns; ns Depression: ns; 0.50 Anxiety: ns; ns Pain intensity: ns; ns	Cohen's *d* Post-treatment; follow-up Guided ACT *v* WL Pain acceptance: 0.59; 0.76 Psychological inflexibility: ns; ns Unguided ACT *v* WL Pain acceptance: ns; ns Psychological inflexibility: ns; ns
Hara, et al (2018)[41]	Effect sizes unavailable in domains of interest	
Scott, et al (2018)[42]	Cohen's *d* 3 month follow-up; 9 month follow-up Average pain: 0.19; 0.10 Pain interference: 0.24; 0.54 Work and social adjustment: 0.45; 0.50 Depression: 0.51; 0.14 ITT 3 month follow-up; 9 month follow-up Average pain: 0.16; 0.11 Pain interference: 0.20; 0.40 Work and social adjustment: 0.47; 0.42 Depression: 0.44; 0.16	Cohen's *d* 3 month follow-up; 9 month follow-up Pain acceptance: 0.87; 0.05 Decentring: 0.42; 0.10 Committed action: 0.26; 0.42 ITT 3 month follow-up; 9 month follow-up Pain acceptance: 0.69; 0.13 Decentring: 0.42; 0.12 Committed action: 0.25; 0.10

Table 2 | Summary of selected effects of comparisons, including ACT versus other comparison conditions or controls *(Continued)*

Author (year)	Effect sizes	
	Outcomes	Psychological flexibility processes
Simister, et al (2018)[43]	Cohen's *d* Post-treatment; 3 month follow-up Fibromyalgia impact: 1.26; 1.59 Depression: 0.87; 0.56 Pain: 0.84; 0.11	Cohen's *d* Post-treatment; 3 month follow-up Pain acceptance: 0.84; 0.80 Mindfulness: 0.29; 0.26 Cognitive fusion: 0.25; 0.65 Valued living: 0.19; 0.46
Wiklund, et al (2018)[44]	Cohen's *d* Completers post-treatment; 6 month follow-up; 12 month follow-up ACT *v* discussion group Pain intensity: 0.14; −0.27; −0.19 ITT completers post-treatment; 6 month follow-up; 12 month follow-up *ACT v discussion group* Pain intensity: −0.05; −0.35; −0.24	None
Dindo, Recober, et al (2020)[45]	Cohen's *d* 3-month follow up; 6 month follow-up Headache disability: 0.44; 0.48 Anxiety: 0.73; 0.74 Quality of life—psych wellbeing: 0.46; 0.44 General disability: 0.33; 0.23	None
Dindo, Johnson, et al (2020)[46]	Cohen's *d* 3 month follow-up Disability: 0.30 Pain severity: 0.10 Pain interference: −0.78	Cohen's *d* 3 month follow-up Psychological flexibility: 0.56
Roslyakova, et al (2020)[50]	Cohen's *d* Post-treatment; post to follow-up Anxiety: −0.64; 0.20 Depression: −0.58; 0.48 Pain: 0.16; 0.25	Cohen's *d* Post-treatment; post to follow-up Pain acceptance: 0.44; 0.16 Psychological inflexibility: 0.23; 0.10
Taheri, et al (2020)[47]	η_p^2 Post-treatment Pain intensity: 0.13	η_p^2 Post-treatment Pain acceptance: 0.25
Vasiliou, et al (2020)[48]	η_p^2 Overall General disability: 0.09 Pain severity: 0.04 Anxiety: <0.01 Depression: 0.05	η_p^2 Overall Pain acceptance: 0.14 Pain fusion: 0.13 Pain avoidance: 0.12 Committed action: 0.01 Value progress: 0.01 Value obstructions: 0.04 Mindfulness: 0.02
Vowles, et al (2020)[49]	Cohen's *d* 6 month follow-up Pain interference: 0.79 Pain intensity: 1.08	None
Rickardsson, et al (2021)[51]	Cohen's *d* Post-treatment Pain interference: 0.99 Quality of life: 0.49 Anxiety: 0.62 Depression: 0.68 Pain intensity: 1.2	Cohen's *d* Post-treatment Psychological inflexibility: 1.0 Value progress: 0.63 Value obstruction: 0.69

ns=effect sizes for non-significant effects not reported; effect size (ES) signs are reversed from original manuscript in some cases to be consistent across all studies. Positive ES indicate superiority of ACT *v* control. CPAQ=chronic pain acceptance questionnaire; GACT=group ACT; ITT=intention to treat analyses; RPT=recommended pharmacological treatment; WL=waiting list.

Considering the median from the range of available effects for each domain, from the 23 available studies, across all comparisons, ACT does not generally appear to produce a significant reduction of pain or anxiety. Evidence shows, however, that it produces benefits in the form of meaningful reductions in pain interference, disability, and depression, and an increase in quality of life. The evidence is strongest for pain interference where the effect is likely to be

medium. Good evidence suggests that ACT leads to increased acceptance of pain and probably to improved psychological flexibility/inflexibility overall, or in other individual facets. Taken together, the benefits of ACT for chronic pain appear similar to traditional CBT, but the evidence for change in the theoretically specified process of change in ACT appears stronger than similar evidence for traditional CBT. These processes of change warrant

further investigation, but more positive evidence supports processes of change in trials of ACT than would be seen in studies of traditional CBT.[19]

Long term outcomes (>12 months)

Follow-up results are most frequently assessed at three or six months. Evidence shows that results at these follow-ups are beneficial, and usually reflect no loss of effect on average. In a trial (n=113) of an internet delivered treatment conducted in Sweden, improvements in favor of ACT, compared with a wait list, were shown for pain, pain interference, depression, anxiety, and insomnia, and all these improvements were maintained at 12 months. This was shown by significant medium to large within group effects at 12 months, ranging from d=0.58 to 1.2, for all of these outcomes, with the exception of anxiety, and no significant decrease in outcomes during the follow-up interval at p<0.05.[51 52] An earlier trial (n=115) compared use of a self-help workbook supported by a therapist with applied relaxation, an established psychological treatment.[30] While the applied relaxation arm did not produce significant effects over time for pain, daily functioning, satisfaction with life, or pain acceptance, the ACT condition did. This was based on within group effects of d=0.37, 0.46, 0.75, and 1.1, respectively, and included small to medium effects at 12 months, range from d=0.47 to 0.74, with the exception of daily functioning which was significantly improved at six months but not at 12 months. Both treatments produced significant improvements in depression and anxiety at 12 months. These significant results are based on calculation of 95% confidence intervals. Additional evidence from an uncontrolled cohort study from a National Health Service specialty pain service (n=108) showed evidence for good outcome results three years after treatment, such as sustained improvements in physical and emotional functioning and a 64.8% rate of cases showing reliable improvement.[53]

Cost effectiveness

Ultimately, treatment resources are not unlimited. Responsible commissioning and delivery of services must consider benefits, risks, and costs to maximize population health overall. Three of the included RCTs in this review addressed cost effectiveness of ACT for chronic pain. These studies show mainly supportive results for ACT, including the following: (a) support for cost effectiveness of ACT compared with applied relaxation for chronic pain at post treatment and three months later, but not six months later, in Sweden,[54] (b) support for cost effectiveness of group ACT compared with both wait list or recommended pharmacology for fibromyalgia, in Spain,[55] and (c) support for cost effectiveness for unguided online ACT compared with a wait list or guided online ACT for chronic pain, in Germany.[56] Results such as these need careful interpretation as the results from studies of cost effectiveness are highly dependent on local or national circumstances, healthcare systems, and prevailing costs.

Processes of change

Analyses of process of change aim to identify the specific mechanisms of therapeutic action that are responsible for producing positive outcomes from treatments. Results from these analyses, typically termed mediation analyses, show whether treatments operate in a theoretically consistent fashion, and produce benefits that are treatment specific.[57] Such results also are expected to fuel future development and improvement of treatments. Six of the RCTs included in this review included analyses of mediation. These focused on either chronic pain from whiplash associated disorder,[58] fibromyalgia,[35] or mixed chronic pain disorders.[59 -62] The ACT based treatments included individual, face-to-face,[58] group

face-to-face,[35 60] a self-help workbook plus weekly telephone sessions,[59] and online treatment.[61 62] While three of these studies included a wait list control,[58 61 62] two of these were three-arm trials that also included expressive writing[62] and unguided internet based ACT.[61] Another three-arm trial included recommended pharmacological treatment or a wait list.[35] Two trials included applied relaxation as a comparison.[59 60]

All the mediation studies were successful in the sense that significant results related to processes of change were found for many of the key outcomes included in trials of ACT. These results showed an important role for processes of change in psychological flexibility in relation to outcomes for pain related disability and life satisfaction,[58] pain interference and emotional distress,[61 62] and physical functioning.[59]

The studies of mediation or processes of change reviewed here also compared the relative strength of theoretically consistent and inconsistent change processes. In these analyses, psychological flexibility or inflexibility appeared as superior or better fitting processes of change compared with pain,[58 60] kinesiophobia, or self-efficacy,[58] anxiety or depression,[58 59] or pain catastrophizing.[60 62] The consistent finding in five of six studies is for a significant predominant role in ACT of theoretically consistent and not theoretically inconsistent processes of therapeutic change. Hence, ACT appears to deliver outcomes specifically via the mechanisms of action by which it is meant to deliver them.

Moderators and predictors of outcome

An important questions to answer when assigning a treatment is for whom is this treatment known to be effective? Answers to this question come from studies of what is called "moderators" or predictors.[63] Information on moderators and predictors is needed to effectively assign, customize, or tailor treatments to maximize individual benefits. We were able to identify just three studies from within the included trials here that addressed moderation or prediction of outcome.[64 -66] In two trials, both involving internet based treatment, participants with better emotional functioning and wellbeing and better psychological flexibility appear to achieve better results in ACT.[65 66] In the other study of moderation, depression was not associated with treatment response.[64] Quite consistently, here and in other studies, demographic or pain related factors appear to play little part in relation to differential outcomes from treatments like ACT[63]—although there is at least one exception,[64] in which age was a significant moderator. Results in the wider literature are consistently inconclusive, and failure to identify factors that can be used to predict outcome, and assign the most suitable treatment, seems to be the modal result; therefore caution is advised in attempting to apply the few findings reviewed here.

Comparison with other recent reviews

The latest systematic review and meta-analysis of psychological treatments for chronic pain was published in 2020, and was based on 59 studies. It found that relative to active control conditions, traditional CBT showed very small benefits for pain, disability, and distress, and when compared with treatment as usual, CBT showed small benefits in each of these domains.[19] This same review included five trials of ACT. This is because the search included studies no later than 16 April 2020, they did not include internet based treatments, or treatments of headache, and they excluded any study with fewer than 20 participants per arm at the end of treatment. The authors concluded there was "no evidence of efficacy or safety" for ACT.[19] While this result is understandable given the methods they used, their conclusion is inconsistent with at least two other

published systematic review and meta-analyses explicitly focused on ACT for chronic pain that found evidence for efficacy. [9] [10] These reviews reported significant benefits from ACT across several key clinical domains, including pain, interference, and distress. It is also inconsistent with a meta-analysis of 66 experimental laboratory studies of components of psychological flexibility, the set of processes underlying ACT,[67] and a review of 20 meta-analyses that included pain.[68] The former found support for the theoretically consistent effects of ACT methods, and the latter found benefits of ACT for a wide range of conditions, including pain, based on a meta-analysis of meta-analyses, including 20 meta-analyses reporting 100 controlled effect sizes from 12 477 participants. The current review is much more inclusive than the earlier ones, particularly with the addition of relatively larger sized internet based trials and trials of headache.

Our review has its own limitations. We exercised no control over quality of studies included, other than to require random allocation to treatments, and to determine that criteria for population, treatment, and outcomes were met. For example, many of the studies we included were small, designed as pilot studies, and some had significant dropout rates. This review was not pre-registered.

Practical implications of available evidence

The evidence reviewed here for ACT is supportive. The average patient with chronic pain benefits, particularly in domains of pain related interference, disability, and depression, but less so in pain itself or anxiety. The outcomes appear neither superior nor inferior to CBT in general. Healthcare providers can be assured that benefits of ACT are specific in that they appear to be associated with their own theoretically based therapeutic processes of change. In terms of who is best suited to ACT in particular, the results on this are not strong or consistent enough to determine. Because success or failure cannot be predicted adequately before treatment, we recommended that patient informed choice be considered as a guide. In particular, insufficient clear evidence is available to exclude people from treatment with ACT based on age, gender, education, pain condition, or baseline level of distress. Evidence for ACT emerges from studies with treatment characteristics such as multiple delivery modalities, group, individual, face to face, and online, therefore, benefits from ACT may be expected from any of these modalities, until demonstrated otherwise. Again, patient choice or local availability may dictate what is accessed.

Emerging treatments

Emerging trends in psychological treatments for chronic pain include attempts to design treatments based on the most effective component methods,[69] or they focus on comorbid conditions associated with chronic pain. For the latter, the focus is on behavioral activation for depression in the context of chronic pain,[70] a combination of ACT plus mindfulness based prevention of relapse in problematic opioid use,[49] or the addition of prolonged exposure to traumatic reminders for people with chronic pain and post-traumatic stress disorder (PTSD).[71] The clinical trial for the study focused on depression is registered and recruitment has started (ClinicalTrials.gov, NCT04140838). For the treatment focused on problematic opioid use in chronic pain, an initial feasibility and preliminary efficacy study (n=35) has been completed and compares the integrated treatment with treatment as usual in military veterans. Recruitment fell below the feasibility target but retention and completion were good. The study produced medium sized effects that favor the integrated treatment for current opioid use and pain interference, and large effects for pain and opioid dose.[49] A fully powered efficacy study is under way that uses an active education

comparator (ClinicalTrials.gov, NCT04648228). The treatment for PTSD in chronic pain has been evaluated in a single case experimental design study (n=4) but has not been further examined. In the single case study, each of the four cases showed clinically relevant improvements in symptoms of PTSD and beliefs related to trauma.[71] These new approaches that include comorbid problems are not "one size fits all" packages of treatment components delivered as a whole for everyone meeting entry criteria for treatment. The developments are not entirely new treatments with novel mechanisms of change, but they do represent new modular designs built from known components.

Other emerging treatments focus on ease of implementation and access. One example is a one session, two hour targeted education session focused on decreasing catastrophizing in relation to chronic pain.[72] Recruitment has been completed for this trial, which compared treatment with either eight weeks of CBT or a two hour health education session, and we await the report of their results (ClinicalTrials.gov, NCT03167086). Treatments like this, and also the wider variety of online treatments now being developed, will be important to address what is called the "treatment gap"—the disconnect between the treatments demonstrated in research settings as evidence based but not delivered by clinicians, or available to those in need in clinical care.[73]

Guidelines

Numerous clinical practice guidelines are relevant to chronic pain. Some focus only on specific conditions, such as low back pain.[74] Others are more general, such as guidance from the National Institute for Health and Care Excellence (NICE[75]) in the UK. Recent NICE guidelines are notable in this review. They are particularly distinct in their emphasis on non-pharmacological approaches. They recommend group exercise and encouragement to stay active. They also recommend that professionals, commissioners, providers, and patients consider ACT or CBT, and consider antidepressant medications. They recommend against anticonvulsants, non-steroidal anti-inflammatory drugs, benzodiazepines, opioids, or paracetamol, among other medications. They recommend against the use of TENS, ultrasound, and interferential therapy, but acupuncture is recommended as "consider."[75] The NICE guidelines are typically highly influential around the world as they are considered rigorously evidence based.

Another example is the Inter-agency Task Force report on pain management best practices from the United States Department of Health and Human Services (DHHS).[76] These guidelines are much more accepting of medications, stating "Various classes of medications, including non-opioids and opioids, should be considered for use." In fact, in this report some effectiveness is claimed for each of the medications explicitly excluded by NICE. These guidelines clearly recommend a multidisciplinary approach that includes recommendations for behavior therapy, CBT, ACT, mindfulness based stress reduction, or biofeedback. NICE recommends against this latter option. (sounded a bit Yoda-ish!)

The difference between these two guidelines appears to reflect their methodology. NICE lays emphasis on "best available evidence," while the DHHS favors consensus of multiple stakeholders. The latter clearly considers "relevant scientific and medical literature," and also expressly emphasizes "patient centered care." In this spirit, the department's report included patient testimonials and input during public meetings, including around 6000 comments.[76] Compared with the DHHS guidelines, the NICE guidelines were published more recently, and lay a greater emphasis on non-pharmacological approaches.[75]

Future developments

Comparing clinical outcomes of ACT versus traditional CBT, or any other treatment, based on group averages is not likely to substantially improve our understanding of how to help individuals. Group data probably miss the point and "therapy type" is too coarse as a unit of analysis.

In future, CBT for chronic pain seems likely to include a greater focus on (a) individual needs rather than syndromal classification, (b) mediation and moderation analyses rather than simply treatment outcome, (c) processes of change rather than therapy types, and on therapy that is process driven rather than protocol driven, and (d) collection and analysis of intensive individual data over time rather than RCTs and aggregated group data.[79 -81] In practice, future forms of CBT probably will not be applied exclusively for low back pain, fibromyalgia, migraine, and the like, or a diagnosis of depression or anxiety disorder for that matter. Instead they are likely to include an individual functional analysis of the person's unique goals, behavior patterns, and a consideration of potential empirically based processes of change, with treatment methods delivered in a dynamically tailored way based on ongoing tracking of relevant processes and outcomes, probably through the use of handheld digital devices such as smart phones.[81 83 84] In the meantime, empirically based processes of change might include variables such as pain catastrophizing, self-efficacy, avoidance, facets of psychological flexibility, and others, preliminarily, such as self-compassion or components of mindfulness.[77]

The assessment of processes of interest is likely to include physiological variables or biomarkers as a supplement to self-report.[70 85 86] Particularly for research related to psychological flexibility and processes of change, a wide range of dimensions is important, including genetic, epigenetic, neurobiological, immune, and others, in part because these can be assessed with relative precision and are known to correlate with the psychological processes or interest, but also because these can help integrate behavioral science with other health related sciences.[87]

Another development that is probable is increasing use of ecological momentary assessment (EMA). Such methods are more direct in time and situation, can obtain finer grained data that show patterns over time, can be sensitive to context, and avoid biases, such as recall bias, that plague conventional self-report measures.[88] Such methods are increasingly used in chronic pain studies[88] but we know from a recent scoping review that EMA is rarely if ever used in treatment outcome studies of psychological treatments for chronic pain so far.[89] These methods are particularly well suited to examining individual processes of change in treatment.

A vision for the future is to end divisions between schools of thought and therapy types and instead integrate around a focus on process of change known to drive improved outcomes and the methods known to impact on these processes. This is the essence of process based therapy.[77 80] This may lead to a time when we do not divide therapies into behavior therapy, CBT, or ACT to determine the degree to which benefits are achieved. ACT is in fact a prototype of process based therapy, as it is not defined mainly by a method set but by a guiding process based model,—namely, psychological flexibility.

Individualized process based therapy rooted in analyses of individual data are already becoming reality. Tailored online ACT self-help for mental health, based on EMA data, is shown to be more efficacious compared with randomly delivered modules or EMA only.[90 91] It has also been demonstrated in a study including a replicated single case experimental design that, for cognitive functional therapy for chronic low back pain and fear avoidance,

multiple potential processes of change appear to play their role in highly individual ways, with a different set of key mediators in each case.[92]

Conclusion

Psychological treatments, typically forms of CBT, have been applied to chronic pain for more than 50 years. The latest generation of CBT is particularly distinctive in moving away from a predominant focus on changing thoughts and feelings as a way to improve symptoms, and toward more integrative processes including mindfulness, acceptance, and psychological flexibility, as ways to improve performance and wellbeing.

ACT, one of the most frequently applied newer generation forms of CBT, produces benefits for people with chronic pain, including improvement in pain interference, disability, depression, and quality of life. The evidence for benefits in pain reduction or for effects on anxiety is lacking, but good evidence shows that ACT methods produce effects on outcomes via theoretically consistent mechanisms of action, or mediators. Reasonably good evidence shows that benefits last, and that this approach may be cost effective.[93] One of the weaker areas of current evidence concerns who is likely to benefit from ACT, the kind of evidence needed to deliver treatment personalized to the individual. These results appear to hold without regard to whether ACT is delivered face to face, in groups, or via online content. Generally speaking, ACT appears neither inferior nor superior to traditional CBT based on current evidence. Additional evidence seems unlikely to change the conclusion that ACT is beneficial for people with chronic pain. Additional studies could focus on improving the delivery of ACT, possibly as a way to produce more consistent results, or research methods could be directed toward answering questions around how to create better impacts on relevant processes of change or how to better individualize delivery. More small sized studies are not needed, nor studies that merely repeat treatment designs and research methods already well studied. Studies should address new questions, seek to understand current heterogeneity in results, systematically incorporate treatment innovations, isolate treatment effects with methods that carry a low risk of bias, and identify mechanisms of change.

A wider view of the evolution of CBT suggests that ACT is not the final form that these treatments will take, but a step along a path. The future of CBT may lie in what is called process based therapy, ushered in by the latest generation developments. If so, this may emerge as an integration and not a competition of therapy types, with a greater focus on processes of change, and on individualizing treatments, based on research methods more suited to understanding the experience and needs of individual people.

Questions for future research

- When people benefit from treatment, what are the key mechanisms of change that make that happen?

- Will idiographic approaches to mechanisms of change in psychological treatments more effectively map these process as compared with what emerges from group based RCTs?

- Are completely individualized psychological treatments likely to be more clinically effective and cost effective than non-individualized "one size fits all" treatments?

- Is it necessary to directly specifically target significant comorbid conditions that appear with chronic pain or will they resolve with effective treatment for the chronic pain?

1   Treede R-D, Rief W, Barke A, etal. Chronic pain as a symptom or a disease. *Pain* 2019;160:19-27. doi: 10.1097/j.pain.0000000000001384 pmid: 30586067

2   Nicholas M, Vlaeyen JWS, Rief W, etalIASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain* 2019;160:28-37. doi: 10.1097/j.pain.0000000000001390 pmid: 30586068

3   Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull* 2007;133:581-624. doi: 10.1037/0033-2909.133.4.581 pmid: 17592957

4   Turk DC, Dworkin RH, Revicki D, etal. Identifying important outcome domains for chronic pain clinical trials: an IMMPACT survey of people with pain. *Pain* 2008;137:276-85. doi: 10.1016/j.pain.2007.09.002 pmid: 17937976

5   Edwards RR, Dworkin RH, Sullivan MD, etal. The role of psychosocial processes in the development and maintenance of chronic pain disorders. *J Pain* 2016;17:70-92doi: 10.1016/j.jpain.2016.01.001.

6   McCracken LM, Morley S. The psychological flexibility model: a basis for integration and progress in psychological approaches to chronic pain management. *J Pain* 2014;15:221-34. doi: 10.1016/j.jpain.2013.10.014 pmid: 24581630

7   Scott W, Hann KEJ, McCracken LM. A comprehensive examination of changes in psychological flexibility following acceptance and commitment therapy for chronic pain. *J Contemp Psychother* 2016;46:139-48. doi: 10.1007/s10879-016-9328-5 pmid: 27397934

8   Zale EL, Lange KL, Fields SA, Ditre JW. The relation between pain-related fear and disability: a meta-analysis. *J Pain* 2013;14:1019-30. doi: 10.1016/j.jpain.2013.05.005 pmid: 23850095

9   Veehof MM, Trompetter HR, Bohlmeijer ET, Schreurs KM. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cogn Behav Ther* 2016;45:5-31. doi: 10.1080/16506073.2015.1098724 pmid: 26818413

10 Hughes LS, Clark J, Colclough JA, Dale E, McMillan D. Acceptance and commitment therapy (ACT) for chronic pain: a systematic review and meta-analysis. *Clin J Pain* 2017;33:552-68. doi: 10.1097/AJP.0000000000000425 pmid: 27479642

11 Dahlhamer J, Lucas J, Zelaya C, etal. Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018;67:1001-6. doi: 10.15585/mmwr.mm6736a2 pmid: 30212442

12 Mills SEE,Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. *Br J Anaesth* 2019;123:e273-83. doi: 10.1016/j.bja.2019.03.023 pmid: 31079836

13 Reid KJ, Harker J, Bala MM, etal. Epidemiology of chronic non-cancer pain in Europe: narrative review of prevalence, pain treatments and pain impact. *Curr Med Res Opin* 2011;27:449-62. doi: 10.1185/03007995.2010.545813 pmid: 21194394

14 Racine M. Chronic pain and suicide risk: A comprehensive review. *Prog Neuropsychopharmacol Biol Psychiatry* 2018;87(Pt B):269-80. doi: 10.1016/j.pnpbp.2017.08.020 pmid: 28847525

15 Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006;10:287-333. doi: 10.1016/j.ejpain.2005.06.009 pmid: 16095934

16 Wu A, March L, Zheng X, etal. Global low back pain prevalence and years lived with disability from 1990 to 2017: estimates from the Global Burden of Disease Study 2017. *Ann Transl Med* 2020;8:299. doi: 10.21037/atm.2020.02.175 pmid: 32355743

17 Abbafati C, Machado DB, Cislaghi B, etalGBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396:1204-22. doi: 10.1016/S0140-6736(20)30925-9 pmid: 33069326

18 Hogan ME, Taddio A, Katz J, Shah V, Krahn M. Health utilities in people with chronic pain using a population-level survey and linked health care administrative data. *Pain* 2017;158:408-16. doi: 10.1097/j.pain.0000000000000776 pmid: 27902568

19 Williams ACC, Fisher E, Hearn L, Eccleston C. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev* 2020;8:CD007407.pmid: 32794606

20 Hayes SC. Acceptance and commitment therapy and the new behavior therapies: mindfulness, acceptance, and relationship. In: Hayes SC, Follette VM, Linehan MM, eds. Mindfulness and acceptance: Expanding the cognitive-behavioral tradition. Guildford Press 2004.1-29.

21 Dimidjian S, Arch JJ, Schneider RL, Desormeau P, Felder JN, Segal ZV. Considering meta-analysis, meaning, and metaphor: a systematic review and critical examination of "third wave" cognitive and behavioral therapies. *Behav Ther* 2016;47:886-905. doi: 10.1016/j.beth.2016.07.002 pmid: 27993339

22 Fordyce WE. *Behavioral methods for chronic pain and illness.* CV Mosby, 1976.

23 Turk DC, Meichenbaum D, Genest M. *Pain and behavioral medicine: A cognitive-behavioral perspective.* Guilford Press, 1983.

24 Hayes S, Strosahl K, Wilson K. *Acceptance and commitment therapy: The process and practice of mindful change.* 2nd ed. Guilford Press, 2012.

25 Hayes SC, Strosahl KD, Wilson KG. *Acceptance and Commitment Therapy: The process and practice of mindful change.* 2nd ed. Guilford Press, 2012.

26 Cherry KM, Hoeven EV, Patterson TS, Lumley MN. Defining and measuring "psychological flexibility": A narrative scoping review of diverse flexibility and rigidity constructs and perspectives. *Clin Psychol Rev* 2021;84:101973. doi: 10.1016/j.cpr.2021.101973 pmid: 33550157

27 Buhrman M, Skoglund A, Husell J, etal. Guided internet-delivered acceptance and commitment therapy for chronic pain patients: a randomized controlled trial. *Behav Res Ther* 2013;51:307-15. doi: 10.1016/j.brat.2013.02.010 pmid: 23548250

28 Dahl J, Wilson KG, Nilsson A. Acceptance and commitment therapy and the treatment of persons at risk for long-term disability resulting from stress and pain symptoms: A preliminary randomized trial. *Behav Ther* 2004;35:785-801doi: 10.1016/S0005-7894(04)80020-0.

29 Wicksell RK, Ahlqvist J, Bring A, Melin L, Olsson GL. Can exposure and acceptance strategies improve functioning and life satisfaction in people with chronic pain and whiplash-associated disorders (WAD)? A randomized controlled trial. *Cogn Behav Ther* 2008;37:169-82. doi: 10.1080/16506070802078970 pmid: 18608312

30 Thorsell J, Finnes A, Dahl J, etal. A comparative study of 2 manual-based self-help interventions, acceptance and commitment therapy and applied relaxation, for persons with chronic pain. *Clin J Pain* 2011;27:716-23. doi: 10.1097/AJP.0b013e318219a933 pmid: 21540740

31 Wetherell JL, Afari N, Rutledge T, etal. A randomized, controlled trial of acceptance and commitment therapy and cognitive-behavioral therapy for chronic pain. *Pain* 2011;152:2098-107. doi: 10.1016/j.pain.2011.05.016 pmid: 21683527

32 Mo'tamedi H, Rezaiemaram P, Tavallaie A. The effectiveness of a group-based acceptance and commitment additive therapy on rehabilitation of female outpatients with chronic headache: preliminary findings reducing 3 dimensions of headache impact. *Headache* 2012;52:1106-19. doi: 10.1111/j.1526-4610.2012.02192.x pmid: 22712503

33 Wicksell RK, Kemani M, Jensen K, etal. Acceptance and commitment therapy for fibromyalgia: a randomized controlled trial. *Eur J Pain* 2013;17:599-611. doi: 10.1002/j.1532-2149.2012.00224.x pmid: 23090719

34 McCracken LM, Sato A, Taylor GJ. A trial of a brief group-based form of acceptance and commitment therapy (ACT) for chronic pain in general practice: pilot outcome and process results. *J Pain* 2013;14:1398-406. doi: 10.1016/j.jpain.2013.06.011 pmid: 24035351

35 Luciano JV, Guallar JA, Aguado J, etal. Effectiveness of group acceptance and commitment therapy for fibromyalgia: a 6-month randomized controlled trial (EFFIGACT study). *Pain* 2014;155:693-702. doi: 10.1016/j.pain.2013.12.029 pmid: 24378880

36 Kemani MK, Olsson GL, Lekander M, Hesser H, Andersson E, Wicksell RK. Efficacy and cost-effectiveness of acceptance and commitment therapy and applied relaxation for longstanding pain: A randomized controlled trial. *Clin J Pain* 2015;31:1004-16. doi: 10.1097/AJP.0000000000000203 pmid: 25585272

37 Pincus T, Anwar S, McCracken LM, etalOBI Trial Management Team. Delivering an Optimised Behavioural Intervention (OBI) to people with low back pain with high psychological risk; results and lessons learnt from a feasibility randomised controlled trial of Contextual Cognitive Behavioural Therapy (CCBT) vs. Physiotherapy. *BMC Musculoskelet Disord* 2015;16:147. doi: 10.1186/s12891-015-0594-2 pmid: 26076755

38 Trompetter HR, Bohlmeijer ET, Veehof MM, Schreurs KM. Internet-based guided self-help intervention for chronic pain based on Acceptance and Commitment Therapy: a randomized controlled trial. *J Behav Med* 2015;38:66-80. doi: 10.1007/s10865-014-9579-0 pmid: 24923259

39 Alonso-Fernández M, López-López A, Losada A, González JL, Wetherell JL. Acceptance and commitment therapy and selective optimization with compensation for institutionalized older people with chronic pain. *Pain Med* 2016;17:264-77.pmid: 26304771

40 Lin J, Paganini S, Sander L, etal. An internet-based intervention for chronic pain: A three-arm randomized controlled study of the effectiveness of guided and unguided acceptance and commitment therapy. *Dtsch Arztebl Int* 2017;114:681-8.pmid: 29082858

41 Hara KW, Bjørngaard JH, Brage S, etal. Randomized controlled trial of adding telephone follow-up to an occupational rehabilitation program to increase work participation. *J Occup Rehabil* 2018;28:265-78. doi: 10.1007/s10926-017-9711-4 pmid: 28597308

42 Scott W, Chilcot J, Guildford B, Daly-Eichenhardt A, McCracken LM. Feasibility randomized-controlled trial of online Acceptance and Commitment Therapy for patients with complex chronic pain in the United Kingdom. *Eur J Pain* 2018;22:1473-84. doi: 10.1002/ejp.1236 pmid: 29704880

43 Simister HD, Tkachuk GA, Shay BL, Vincent N, Pear JJ, Skrabek RQ. Randomized controlled trial of online acceptance and commitment therapy for fibromyalgia. *J Pain* 2018;19:741-53. doi: 10.1016/j.jpain.2018.02.004 pmid: 29481976

44 Wiklund T, Linton SJ, Alföldi P, Gerdle B. Is sleep disturbance in patients with chronic pain affected by physical exercise or ACT-based stress management? - A randomized controlled study. *BMC Musculoskelet Disord* 2018;19:111. doi: 10.1186/s12891-018-2020-z pmid: 29631567

45 Dindo LN, Recober A, Calarge CA, etal. One-day acceptance and commitment therapy compared to support for depressed migraine patients: a randomized clinical trial. *Neurotherapeutics* 2020;17:743-53. doi: 10.1007/s13311-019-00818-0 pmid: 31863406

46 Dindo L, Johnson AL, Lang B, Rodrigues M, Martin L, Jorge R. Development and evaluation of an 1-day Acceptance and Commitment Therapy workshop for Veterans with comorbid chronic pain, TBI, and psychological distress: Outcomes from a pilot study. *Contemp Clin Trials* 2020;90:105954. doi: 10.1016/j.cct.2020.105954 pmid: 32032736

47 Taheri AA, Foroughi AA, Mohammadian Y, etal. The effectiveness of acceptance and commitment therapy on pain acceptance and pain perception in patients with painful diabetic neuropathy: a randomized controlled trial. *Diabetes Ther* 2020;11:1695-708. doi: 10.1007/s13300-020-00851-9 pmid: 32533548

48 Vasiliou VS, Karademas EC, Christou Y, Papacostas S, Karekla M. Acceptance and commitment therapy for primary headache sufferers: A randomized controlled trial of efficacy. *J Pain* 2021;22:143-60. doi: 10.1016/j.jpain.2020.06.006 pmid: 32682815

49 Vowles KE, Witkiewitz K, Cusack KJ, etal. Integrated behavioral treatment for veterans with co-morbid chronic pain and hazardous opioid use: a randomized controlled pilot trial. *J Pain* 2020;21:798-807. doi: 10.1016/j.jpain.2019.11.007 pmid: 31760109

50 Roslyakova T, Falco MA, Gauchet A. An exploratory clinical trial on acceptance and commitment therapy as an adjunct to psychoeducational relaxation therapy for chronic pain. *Psychol Health* 2021;36:1403-26. doi: 10.1080/08870446.2020.1856844 pmid: 33297730

51 Rickardsson J, Gentili C, Holmström L, etal. Internet-delivered acceptance and commitment therapy as microlearning for chronic pain: A randomized controlled trial with 1-year follow-up. *Eur J Pain* 2021;25:1012-30. doi: 10.1002/ejp.1723 pmid: 33460240

52 Rickardsson J, Zetterqvist V, Gentili C, etal. Internet-delivered acceptance and commitment therapy (iACT) for chronic pain-feasibility and preliminary effects in clinical and self-referred patients. *Mhealth* 2020;6:27. doi: 10.21037/mhealth.2020.02.02 pmid: 32632365

53 Vowles KE, McCracken LM, O'Brien JZ. Acceptance and values-based action in chronic pain: a three-year follow-up analysis of treatment effectiveness and process. *Behav Res Ther* 2011;49:748-55. doi: 10.1016/j.brat.2011.08.002 pmid: 21885034

54 Kemani MK, Olsson GL, Lekander M, Hesser H, Andersson E, Wicksell RK. Efficacy and cost-effectiveness of acceptance and commitment therapy and applied relaxation for longstanding pain: a Randomized Controlled Trial. *Clin J Pain* 2015;31:1004-16. doi: 10.1097/AJP.0000000000000203 pmid: 25585272

55 Luciano JV, D'Amico F, Feliu-Soler A, etal. Cost-utility of group acceptance and commitment therapy for fibromyalgia versus recommended drugs: an economic analysis alongside a 6-month randomized controlled trial conducted in Spain (EFFIGACT Study). *J Pain* 2017;18:868-80. doi: 10.1016/j.jpain.2017.03.001 pmid: 28342891

56 Paganini S, Lin J, Kählke F, etal. A guided and unguided internet- and mobile-based intervention for chronic pain: health economic evaluation alongside a randomised controlled trial. *BMJ Open* 2019;9:e023390. doi: 10.1136/bmjopen-2018-023390 pmid: 30967405

57 Kazdin AE. Mediators and mechanisms of change in psychotherapy research. *Annu Rev Clin Psychol* 2007;3:1-27. doi: 10.1146/annurev.clinpsy.3.022806.091432 pmid: 17716046

58 Wicksell RK, Olsson GL, Hayes SC. Psychological flexibility as a mediator of improvement in Acceptance and Commitment Therapy for patients with chronic pain following whiplash. *Eur J Pain* 2010;14:1059. doi: 10.1016/j.ejpain.2010.05.001 pmid: 20538493

59 Cederberg JT, Cernvall M, Dahl J, von Essen L, Ljungman G. Acceptance as a mediator for change in acceptance and commitment therapy for persons with chronic pain?*Int J Behav Med* 2016;23:21-9. doi: 10.1007/s12529-015-9494-y pmid: 26041582

60 Kemani MK, Hesser H, Olsson GL, Lekander M, Wicksell RK. Processes of change in acceptance and commitment therapy and applied relaxation for long-standing pain. *Eur J Pain* 2016;20:521-31. doi: 10.1002/ejp.754 pmid: 26684472

61 Lin J, Klatt LI, McCracken LM, Baumeister H. Psychological flexibility mediates the effect of an online-based acceptance and commitment therapy for chronic pain: an investigation of change processes. *Pain* 2018;159:663-72. doi: 10.1097/j.pain.0000000000001134 pmid: 29320375

62 Trompetter HR, Bohlmeijer ET, Fox JP, Schreurs KM. Psychological flexibility and catastrophizing as associated change mechanisms during online Acceptance & Commitment Therapy for chronic pain. *Behav Res Ther* 2015;74:50-9. doi: 10.1016/j.brat.2015.09.001 pmid: 26409158

63 Gilpin HR, Keyes A, Stahl DR, Greig R, McCracken LM. Predictors of treatment outcome in contextual cognitive and behavioral therapies for chronic pain: A systematic review. *J Pain* 2017;18:1153-64. doi: 10.1016/j.jpain.2017.04.003 pmid: 28455249

64 Wetherell JL, Petkus AJ, Alonso-Fernandez M, Bower ES, Steiner AR, Afari N. Age moderates response to acceptance and commitment therapy vs. cognitive behavioral therapy for chronic pain. *Int J Geriatr Psychiatry* 2016;31:302-8. doi: 10.1002/gps.4330 pmid: 26216753

65 Probst T, Baumeister H, McCracken LM, Lin J. Baseline psychological inflexibility moderates the outcome pain interference in a randomized controlled trial on internet-based acceptance and commitment therapy for chronic pain. *J Clin Med* 2018;8:24. doi: 10.3390/jcm8010024 pmid: 30585216

66 Trompetter HR, Bohlmeijer ET, Lamers SMA, Schreurs KM. Positive psychological wellbeing is required for online self-help acceptance and commitment therapy for chronic pain to be effective. *Front Psychol* 2016;7:353. doi: 10.3389/fpsyg.2016.00353 pmid: 27014159

67 Levin ME, Hildebrandt MJ, Lillis J, Hayes SC. The impact of treatment components suggested by the psychological flexibility model: a meta-analysis of laboratory-based component studies. *Behav Ther* 2012;43:741-56. doi: 10.1016/j.beth.2012.05.003 pmid: 23046777

68 Gloster AT, Walder N, Levin ME, etal. The empirical status of acceptance and commitment therapy: A review of meta-analyses. *J Contextual Behav Sci* 2020;18:181-92doi: 10.1016/j.jcbs.2020.09.009.

69 Sharpe L, Jones E, Ashton-James CE, Nicholas MK, Refshauge K. Necessary components of psychological treatment in pain management programs: A Delphi study. *Eur J Pain* 2020;24:1160-8. doi: 10.1002/ejp.1561 pmid: 32187442

70 Sanabria-Mazo JP, Forero CG, Cristobal-Narváez P, etal. Efficacy, cost-utility and physiological effects of Acceptance and Commitment Therapy (ACT) and Behavioural Activation Treatment for Depression (BATD) in patients with chronic low back pain and depression: study protocol of a randomised, controlled trial including mobile-technology-based ecological momentary assessment (IMPACT study). *BMJ Open* 2020;10:e038107. doi: 10.1136/bmjopen-2020-038107 pmid: 32709656

71 Åkerblom S, Perrin S, Fischer MR, McCracken LM. Prolonged exposure for pain and comorbid PTSD: a single-case experimental study of a treatment supplement to multiprofessional pain rehabilitation. *Scand J Pain* 2022doi: 10.1515/sjpain-2021-0100.

72 Darnall BD, Ziadni MS, Roy A, etal. Comparative efficacy and mechanisms of a single-session pain psychology class in chronic low back pain: Study protocol for a randomized controlled trial. *Trials* 2018;19:165. doi: 10.1186/s13063-018-2537-3 pmid: 29510735

73 Kazdin AE. Addressing the treatment gap: A key challenge for extending evidence-based psychosocial interventions. *Behav Res Ther* 2017;88:7-18. doi: 10.1016/j.brat.2016.06.004 pmid: 28110678

74 Qaseem A, Wilt TJ, McLean RM, etalClinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: A clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2017;166:514-30. doi: 10.7326/M16-2367 pmid: 28192789

75 National Institute for Health and Care Excellence. Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. 2021. https://www.nice.org.uk/guidance/ng193

76 US Department of Health and Human Services. Pain management: Best practices. 2019. https://www.hhs.gov/sites/default/files/pmtf-final-report-2019-05-23.pdf

77 Hayes SC, Hofmann SG. The third wave of cognitive behavioral therapy and the rise of process-based care. *World Psychiatry* 2017;16:245-6. doi: 10.1002/wps.20442 pmid: 28941087

78 Hayes SC, Levin ME, Plumb-Vilardaga J, Villatte JL, Pistorello J. Acceptance and commitment therapy and contextual behavioral science: examining the progress of a distinctive model of behavioral and cognitive therapy. *Behav Ther* 2013;44:180-98. doi: 10.1016/j.beth.2009.08.002 pmid: 23611068

79 Hayes SC, Hofmann SG, Stanton CE, etal. The role of the individual in the coming era of process-based therapy. *Behav Res Ther* 2019;117:40-53. doi: 10.1016/j.brat.2018.10.005 pmid: 30348451

80 Hofmann SG, Hayes SC. The future of intervention science: Process-based therapy. *Clin Psychol Sci* 2019;7:37-50. doi: 10.1177/2167702618772296. pmid: 30713811

81 Hofmann SG, Curtiss JE, Hayes SC. Beyond linear mediation: Toward a dynamic network approach to study treatment processes. *Clin Psychol Rev* 2020;76:101824. doi: 10.1016/j.cpr.2020.101824 pmid: 32035297

82 Dalgleish T, Black M, Johnston D, Bevan A. Transdiagnostic approaches to mental health problems: Current status and future directions. *J Consult Clin Psychol* 2020;88:179-95. doi: 10.1037/ccp0000482 pmid: 32068421

83 McCracken LM. Necessary components of psychological treatment for chronic pain: More packages for groups or process-based therapy for individuals?*Eur J Pain* 2020;24:1001-2. doi: 10.1002/ejp.1568 pmid: 32227418

84 McCracken LM. Beyond therapy types: Mindful self-compassion and the future of process-based therapy for chronic pain. *Eur J Pain* 2021;25:729-30. doi: 10.1002/ejp.1739 pmid: 33534921

85 Järvelä-Reijonen E, Puttonen S, Karhunen L, etal. The effects of acceptance and commitment therapy (ACT) intervention on inflammation and stress biomarkers: a Randomized Controlled Trial. *Int J Behav Med* 2020;27:539-55. doi: 10.1007/s12529-020-09891-8 pmid: 32394219

86 Aytur SA, Ray KL, Meier SK, etal. Neural mechanisms of acceptance and commitment therapy for chronic pain: a network-based fMRI approach. *Front Hum Neurosci* 2021;15:587018. doi: 10.3389/fnhum.2021.587018. pmid: 33613207

87 Hayes SC, Merwin RM, McHugh L, etal. Report of the ACBS Task Force on the strategies and tactics of contextual behavioral science research. *J Contextual Behav Sci* 2021;20:172-83doi: 10.1016/j.jcbs.2021.03.007.

88 May M, Junghaenel DU, Ono M, Stone AA, Schneider S. Ecological momentary assessment methodology in chronic pain research: a systematic review. *J Pain* 2018;19:699-716. doi: 10.1016/j.jpain.2018.01.006 pmid: 29371113

89 Lavefjord A, Sundström FTA, Buhrman M, etal. *Assessment methods in single case design studies of psychological treatments for chronic pain: a scoping review.* J Context Behav Sci, 2021, doi: 10.1016/j.jcbs.2021.05.005.

90 Levin ME, Navarro C, Cruz RA, Haeger J. Comparing in-the-moment skill coaching effects from tailored versus non-tailored acceptance and commitment therapy mobile apps in a non-clinical sample. *Cogn Behav Ther* 2019;48:200-16. doi: 10.1080/16506073.2018.1503706 pmid: 30117784

91 Levin ME, Haeger J, Cruz RA. Tailoring acceptance and commitment therapy skill coaching in the moment through smartphones: results from a randomized controlled trial. *Mindfulness* 2019;10:689-99doi: 10.1007/s12671-018-1004-2.

92 Caneiro JP, Smith A, Linton SJ, Moseley GL, O'Sullivan P. How does change unfold? an evaluation of the process of change in four people with chronic low back pain and high pain-related fear managed with Cognitive Functional Therapy: A replicated single-case experimental design study. *Behav Res Ther* 2019;117:28-39. doi: 10.1016/j.brat.2019.02.007 pmid: 30853096

93 Feliu-Soler A, Cebolla A, McCracken LM, etal. Economic impact of third-wave cognitive behavioral therapies: a systematic review and quality assessment of economic evaluations in randomized controlled trials. *Behav Ther* 2018;49:124-47. doi: 10.1016/j.beth.2017.07.001 pmid: 29405918