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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)

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ABSTRACT

Introduction The IMPACT study focuses on chronic low back pain (CLBP) and depression symptoms, a prevalent and complex problem that represents a challenge for health professionals. Acceptance and Commitment Therapy (ACT) and Brief Behavioural Activation Treatment for Depression (BATD) are effective treatments for patients with persistent pain and depression, respectively. The objectives of this 12 month, multicentre, randomised, controlled trial (RCT) are (i) to examine the efficacy and cost-utility of adding a group-based form of ACT or BATD to treatment-as-usual (TAU) for patients with CLBP and moderate to severe levels of depressive symptoms; (ii) identify pre–post differences in levels of some physiological variables and (iii) analyse the role of polymorphisms in the *FKBP5* gene, psychological process measures and physiological variables as mediators or moderators of long-term clinical changes.

Methods and analysis Participants will be 225 patients with CLBP and moderate to severe depression symptoms recruited at Parc Sanitari Sant Joan de Déu (St. Boi de Llobregat, Spain) and Hospital del Mar (Barcelona, Spain), randomly allocated to one of the three study arms: TAU vs TAU+ACT versus TAU+BATD. A comprehensive assessment to collect clinical variables and costs will be conducted pretreatment, post-treatment and at 12 months follow-up, being pain interference the primary outcome measure. The following physiological variables will be considered at pretreatment and post-treatment assessments in 50% of the sample: immune-inflammatory markers, hair cortisol and cortisone, serum cortisol, corticosteroid-binding globulin and vitamin D. Polymorphisms in the *FKBP5* gene (rs3800373, rs9296158, rs1360780, rs9470080 and rs4713916) will be analysed at baseline assessment. Moreover, we will include mobile-technology-based ecological momentary assessment, through the Pain Monitor app, to track ongoing clinical status during ACT and BATD treatments. Linear mixed-effects models using restricted maximum likelihood, and a full economic evaluation applying bootstrapping techniques, acceptability curves and sensitivity analyses will be computed.

Ethics and dissemination This study has been approved by the Ethics Committee of the Fundació Sant Joan de Déu and Hospital del Mar. The results will be actively disseminated through peer-reviewed journals, conference presentations, social media and various community engagement activities.

Trial registration number NCT04140838

Strengths and limitations of this study

- This is thought to be the first study comparing the efficacy and cost-utility of Acceptance and Commitment Therapy and Behavioural Activation Treatment for Depression in addition to treatment as usual (TAU) versus TAU alone for the management of comorbid chronic low back pain (CLBP) and depression.
- The IMPACT protocol combines assessment with classical legacy measures and ecological momentary assessment to obtain more precise information on the dynamics of the variables to be assessed.
- Besides self-report measures, this study will include physiological variables such as cortisol, cytokines and vitamin D levels, in order to know the impact of treatments on these stress-related biological variables.
- As far as we know, this study represents the first attempt to explore the predictive role of *FKBP5* gene and distal or proximal stressful experiences in response to psychological treatments for CLBP and depression.
- Blinding of patients and therapists will not be possible. This represents a fundamental problem in randomised controlled trials with psychological treatments.

INTRODUCTION

Recent systematic reviews have estimated that more than 10% of the general population worldwide suffers chronic pain.[1 2] Among chronic pain conditions, chronic low back pain (CLBP) is one of the most prevalent and costly.[3 4] Depression is by far the most common psychiatric problem associated with CLBP.[5 6]

The relationship between pain and depression is bidirectional.[7] Some theories postulate that pain and depression share common physiopathological mechanisms and that one can lead to the other via activation of these mechanisms. This could include mediators of the inflammatory and immune response and the role they play in endogenous nociceptive regulation and affective regulation.[8] In particular, cytokines appear to have a crucial role in chronic pain conditions, so that a high expression of proinflammatory mediators can alter the physiopathology of chronic pain.[9] At the same time, inflammatory mediators of innate immunity and cell-mediated immunity cooperate in the onset and expression of depression.[10] On the other hand, a clear correlation between vitamin D deficiency and the presence of chronic pain and depression has been described in recent years.[11] Vitamin D substantially modulates the inflammatory response by controlling cytokine expression, inhibiting proinflammatory, and increasing anti-inflammatory ones. Vitamin D deficiency could affect the response of patients with chronic pain to the treatments applied.[12–15]

Chronic stress appears to play a pivotal role in mental and physical health and leads to hypothalamic–pituitary–adrenal axis (HPA) dysregulation which in turn impairs the stress response.[16 17] Genetic, epigenetic and early stress exposure, among other factors, shape individual resilience and vulnerability, as well as HPA activity.[18 19] In this regard, the FKB506 binding protein 51 gene (FKBP5) is a critical regulator of glucocorticoid receptor activity (and thus HPA function too) and its interaction with distal and proximal stressors has not been previously examined in comorbid chronic pain and depression. This interaction could be key for understanding the etiological mechanisms involved in such conditions, as well as for identifying potential therapeutic mechanisms.[20–26] In addition, hair cortisol reflecting long-term HPA activity has recently emerged as a potential predictor of treatment response in anxiety and depression.[19]

The therapeutic options available for chronic pain management are very extensive. Interestingly, a number of psychological treatments have shown positive effects at the psychological, neuroendocrine and immune levels in a wide range of pain-related conditions, as well as for depression.[27] These generally comprise forms of Cognitive Behavioural Therapy (CBT), including treatments that focus on mindfulness, and Acceptance and Commitment Therapy (ACT). In a meta-analysis of 11 clinical trials in patients with chronic pain,[28] ACT was better than the control conditions in improving pain acceptance, functional impairment, anxiety, depression and pain intensity. In addition, another form of CBT, Behavioural Activation Treatment for Depression (BATD), has proved to be as effective as classical CBT in reducing depressive symptoms in a meta-analysis.[29]

Both treatments, ACT and BATD, are potentially cost-effective for the management of chronic pain and depression, respectively, according to a recent systematic review carried out by the team of the present project.[30] In our opinion, it is important to demonstrate their cost-utility for the management of a complex problem as relevant as comorbid CLBP and depression, to characterise the psychological and physiological mechanisms through which they exert their therapeutic effect, and identify potential predictors of treatment response.

The objectives of the IMPACT (*Improving Pain and Depression with ACT and BATD*) study are (i) to examine the efficacy and cost-utility of adding ACT or BATD to treatment-as-usual (TAU) in the management of patients with CLBP and moderate to severe depression for improving pain interference (primary outcome) and depressive, anxious and stress symptoms, pain catastrophising and quality of life (secondary outcomes); (ii) to identify pre–post differences in levels of different physiological variables (immune-inflammatory markers, hair cortisol and cortisone, serum cortisol, corticosteroid-binding globulin (CBG) and vitamin D) and correlate these changes with those observed at self-report measures and (iii) analyse the role of polymorphisms in the *FKBP5* gene, psychological process measures and physiological variables as mediators or moderators of long-term clinical changes.

METHODS AND ANALYSIS

Trial design

The RCT protocol has been developed following the Standard Protocol Items: Recommendations for Interventional Trials.[31] For reporting, we will follow the

guidelines of the Consolidated Standards of Reporting Trials (CONSORT)[32] and the Consolidated Health Economic Evaluation Reporting Standards statement.[33] IMPACT is a 12-month multicentre RCT with three treatment arms: TAU, TAU+ACT and TAU+BATD. Therefore, patients in three arms will receive TAU, and ACT and BATD will be complementary treatments to the standard one provided in the Spanish National Health System.

Recruitment strategy

Potential participants are those patients with CLBP diagnosis seeking services currently or in the last 3 years at Parc Sanitari Sant Joan de Déu (St. Boi de Llobregat, Spain) or Hospital del Mar (Barcelona, Spain). These patients will be screened to evaluate their current pain intensity and the Patient Health Questionnaire (PHQ-9) will be administered to confirm the presence of moderate to severe active depression.

Sample size

Sample size was estimated considering a target power of 80%, an alpha level of 0.05 and was calculated taking the primary outcome measure into account (Brief Pain Inventory-Interference Scale (BPI-IS)). The estimate was based on a one-way analysis of variance (followed by Dunn–Bonferroni post-hoc tests) for between-group differences in the change from baseline to subsequent assessment, assuming no systematic baseline or other covariate group differences after randomisation. The minimal clinically significant difference for the BPI-IS is 1 point (SD of improvement of 2 points).[34] This calculation yielded a suggested sample size of 64 patients per study arm. Allowing for a potential attrition rate of 15% our final sample size was 75 participants per group.

Eligibility criteria

All participants will meet the following inclusion criteria: male or female aged 18–70 years; diagnosis of CLBP (≥3 months) according to medical history; pain intensity ≥4 points out of 10 points on a numeric pain rating scale in the past week; moderate to severe depressive symptoms according to PHQ-9 (total score ≥10); fluent in Spanish language and provision of written informed consent to participate (a copy of the consent form is provided as an (online supplementary document). Only participants with a score of at least 60% on the question 'Which situation describes your pain over the past 4 weeks the best? 100% of the pain in the low back; 80% of the pain in the low back and 20% in the leg(s); 60% of the pain in the low back and 40% in the leg(s); 50% of the pain in the low back and 50% in the leg(s); 40% of the pain in the low back and 60% in the leg(s); or 20% of the pain in the low back and 80% in the leg(s)' will be included. With this question, we will be able to differentiate dominant leg pain from dominant CLBP, avoiding the likelihood of recruitment of participants suffering dominant radiculopathy.[35]

Potential participants will be excluded according to the following exclusion criteria (based on previous RCTs):[36] the presence of cognitive impairment; previous (last year) or current psychological treatment; presence of severe psychiatric disorder (eg, psychotic disorder), substance dependence/abuse or presence of degenerative medical disease (eg, Alzheimer's dementia); patients involved in litigation with the health system; patients with scheduled surgical intervention or other interventions and inability to attend group treatment sessions. For the biomarkers substudy (50% of patients in each study arm), the following exclusion criteria will be added: cold/infection symptoms on the day of blood collection; needle phobia; BMI>30 kg/m^2 or weight >110 kg; consumption >8 units of caffeine per day (maximum one drink with caffeine on the day of testing); smoker >5 cigarettes a day; hair length <3 cm, use of glucocorticoid medication or anticytokine drugs and being pregnant or breastfeeding.

Procedure and randomisation

A list of potential participants (with contact telephone number) will be presented to the study team at each centre. This list will pass to the clinicians, so that they carry out the telephone screening and set an appointment for the first face-to-face interview (performed by health psychologists) with all those who agree to participate and meet the eligibility criteria. After obtaining informed written consent, the evaluators will conduct the baseline interview using battery of computer-administered measures. Patients will be contacted again after 3–5 days to obtain peripheral blood and hair samples. These extractions will be performed at a preset time (8.00–9.00 AM) to reduce circadian variability in the levels of the immune and endocrine markers evaluated. In order to limit the effects of medication on the study variables, patients will be asked to refrain from taking analgesic or anti-inflammatory drugs within 72 hours prior to obtaining the biological samples.

Random assignment of participants to study arms will be executed after baseline assessments as recommended by the CONSORT guidelines.[32] Randomisation will be planned and executed by a statistician with no involvement in screening, enrolment or treatment processes. Once written consent and baseline assessment have been completed, study participants will be given a unique personal code and randomised by means of an online randomisation programme. The computer-generated randomisation will apply a permuted block design to ensure that the groups are balanced taking biomarkers substudy eligibility criteria into account. The randomisation list will remain with the clinical trials committee of Fundació Sant Joan de Déu (FSJD) for the full duration of the RCT. This list will be stored in an encrypted file on a password-protected computer in the clinical trials supervisor's office to assure concealment of allocation. Participants' assignments will be communicated to administrative personnel of each centre by the clinical trials supervisor via e-mail. Patients will be informed of

their group allocation by the administrative personnel, who will send a notification in sealed, opaque numbered envelopes.

Two subsequent face-to-face assessments will be carried out at the end of the 8 weeks of treatment (post-treatment) and at 12 months follow-up (56 weeks after randomisation). To obtain the biological samples at post-treatment, the same procedure as in the baseline assessment will be followed. See figure 1 for patients' flow chart.

Treatments

Treatment-as-usual

In Spain, chronic pain management is mainly carried out by general practitioners (GPs) in regular consultations, commonly consisting of face-to-face visits (5–10 min) to monitor the physical and emotional status of the patient. GPs usually provide advice, and prescribe pharmacotherapy (pain medications, hypnotics and antidepressants) or make onward referrals to pain units in hospitals when more specialised pain management procedures are required. The frequency of consultations is based on the type and stage of disease of each patient. For this study, usual care will be the same as in routine daily practice, without any modifications.

Treatment-as-usual+Acceptance and commitment therapy

The ACT treatment component includes, as the name implies, methods to promote acceptance (non-avoidance) of unwanted experiences, and engagement in goal-directed and values-based action. Alternatively, ACT is focused on promoting psychological flexibility, or the ability to develop behaviour patterns *open, aware and engaged*[37] (see table 1). Patients suffering from pain recurrently use avoidance as a coping strategy, and at its most basic level, this therapy is designed to address that by providing a broader set of skills. There is now considerable evidence for the therapeutic model underlying ACT[38] and for the treatment approach itself as applied to chronic pain. Recent meta-analyses supported the effectiveness of ACT in patients with chronic pain.[28 39]

Treatment-as-usual+Behavioural activation treatment for depression

BATD is based on the application of learning principles to the pattern of withdrawn or reduced behaviour activity associated with depression (see table 2). Its objective is to counteract depressive symptoms and, as a consequence, to ensure that patients regain a productive and emotionally satisfying life. Its methodology essentially consists in 'activating' subjects with depression through programming

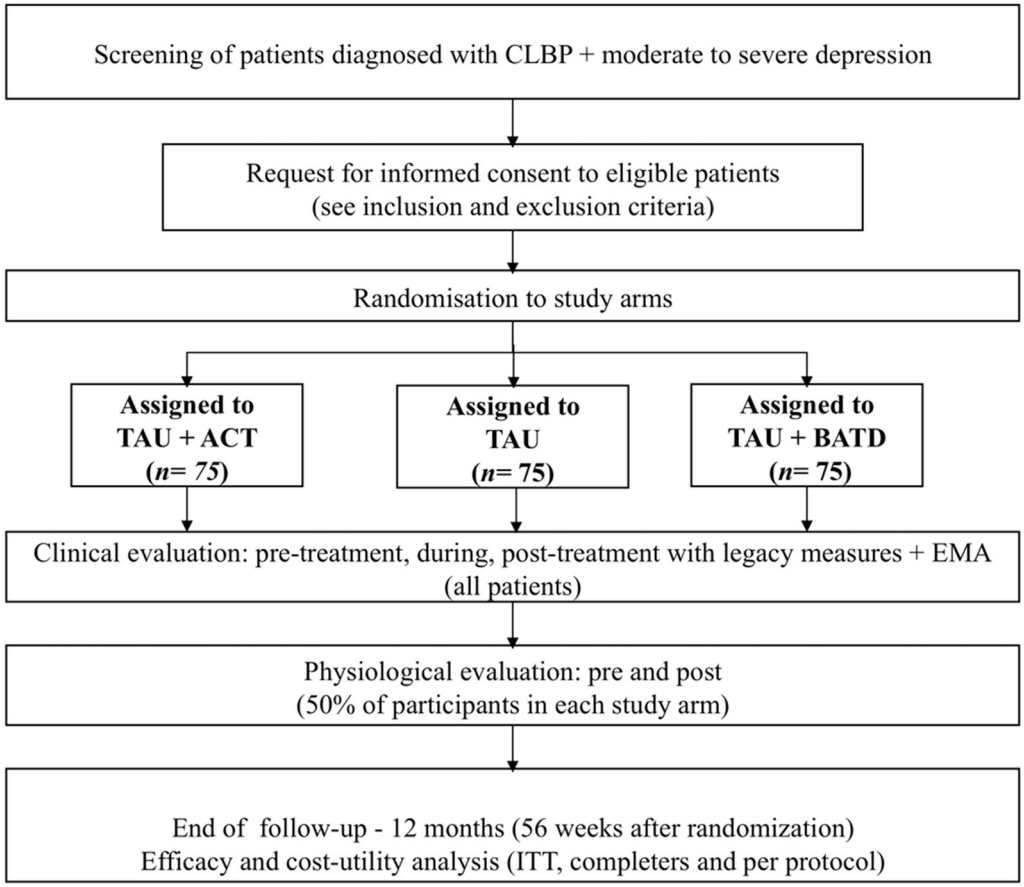

Figure 1 Flowchart of the IMPACT study based on the Consolidated Standards of Reporting Trials guidelines. ACT, Acceptance and Commitment Therapy; BATD, Brief Behavioural Activation Treatment for Depression; CLBP, chronic low back pain; EMA, ecological momentary assessment; ITT, intention-to-treat; TAU, treatment as usual.

Table 1 Outline of ACT group treatment sessions

Session	ACT
1	Participants' and clinician's presentation. Psychoeducation and introduction to ACT (ACT basics; scientific advances in chronic pain and depression management; psychological theories of pain, suffering and stress; stressors, fears and indicators; identification of values; breathing exercises).
2	Value analysis I. Problems of experiential avoidance. Creative hopelessness through metaphors: control is the problem and not the solution. Anxiety, fight and flight, and its effects. Accepting the risk of the life's journey: experiences, feelings and emotions.
3	Value analysis II. Objectives. Laws of thought and consequences of language. Mind and deactivation of thought (cognitive defusion): creating distance with thoughts. Learning meditation techniques and effects. Practicing meditation exercises.
4	Value analysis III. Psychological barriers and obstacles. Emotional distress and its consequences. Emotional phenomena, personality variables and health states. Discovering commitments with committed actions.
5	Values and feelings. Taking the initiative with a 'Plan of action and willingness'. Psychological flexibility, resilience and self-motivation. Expansion and body scan exercises. Learning to relax.
6	Taking a direction. The self as context, process and content. Awareness of the present: 'here and now'. The brain and emotions: managing situations and overwhelming emotional responses.
7	Dare and change: willingness and determination. Self-awareness, assertiveness and self-esteem. Experiential expansion exercises: felt sensations. Happiness according to positive psychology. Benefits of physical exercise: movement.

At the beginning of each session, time will be taken to briefly go over what was discussed in the previous session and every person's weekly records will be collected and briefly commented on.
ACT, Acceptance and Commitment Therapy.

and conduct of behaviours that are likely to increase the experiences of directly positively reinforcing qualities in their current context. A meta-analysis supported the effectiveness of behavioural activation in patients with depression.[29]

Both psychological treatments (ACT and BATD) will be administered in a group format of 8 weekly 1.5 hour sessions. In RCTs of psychological treatment, it is recommend that more than one therapist deliver each treatment to create a more realistic and generalisable impression of

Table 2 Outline of BATD group treatment sessions

Session	Description
1	Participants' and clinician's presentation. Collection of information related with areas of activity and interaction contexts. Delivery of activity log to obtain an accurate assessment of the patient's daily activities, which is useful for: providing a baseline measure and comparing their progress when their activity level increases later in the treatment.
2	Identification of information related to depressive behaviours. Exploration of problematic behaviours and identification of patients' objectives regarding treatment.
3	Obtaining complementary information regarding the characteristics of the history of patient interactions and any contexts and interactions that reinforce depressive behaviours. Establishment of short-term, medium-term and long-term goals.
4	Explanation of the hypotheses of factors associated with the origins, maintenance and therapeutic change of problematic behaviour. In this session, 10 personalised activities are selected according to each person's own needs and desires, without any particular order. With the selected activities, a ranking is then generated that goes from the least difficult to the most difficult activity.
5	Once the 10 target activities have been identified, a record is made to track their progress weekly, including the number of times they would like to complete the activity in a period of 1 week (the ideal frequency). The number of activities varies each week, but they always range between three and five activities.
6	Discussion of what was obtained from the records in general. Exploration of the satisfaction with the activities.
7	Coping abilities. How to approach emotions and reactions to events and responses associated with depression. Relationship between avoidance behaviours and maintenance of difficulties.
8	Examination of new behaviours to be incorporated. Discussion about the goals achieved and the barriers to maintain the weekly activity plan. Farewell.

BATD, Brief Behavioural Activation Treatment for Depression.

effectiveness,[40] so each therapy will be conducted by at least three different therapists. In addition to prior experience delivering ACT or BATD, all therapists will do a 3-hour 'refresher' training prior to starting the RCT with the aim also to assure simultaneous fidelity to the manual with flexibility within sessions. Finally, to monitor treatment fidelity within ACT and BATD, research assistants will video-tape all sessions. Two independent experts in both treatments have been selected for his expertise in the delivery of these therapies. They will rate adherence to treatment using videotapes of therapy sessions. A random sample of tapes, stratified by therapist and therapy session will be rated using the instruments described below.

Study measures

All participants will be assessed with a computer-administered battery of measures, using the software Research Electronic Data Capture (REDCap) (see table 3).

Measures for sociodemographic characteristics, clinical features and screening

Sociodemographic Questionnaire. Information about gender, date of birth, marital status, living arrangements, educational level, income level and employment status.

Clinical data. Ad hoc interview collecting data about history and duration of CLBP and depression symptoms,

Table 3 Time points at which measures and data are collected

Measures	Pre	During	Post	1-year follow-up
Sociodemographic, clinical and screening measures				
Sociodemographic data (gender, date of birth, marital status)	X			
Clinical data (years of evolution, comorbidities)	X			
PHQ-9 (depression symptoms)	X			
CIDI (diagnosis of depression)	X			
CTQ-SF (childhood trauma)	X			
Primary outcome measure				
BPI-IS (pain interference)	X		X	X
Secondary outcome measures				
NRS (pain intensity)	X		X	X
DASS-21 (anxiety, depression and stress)	X		X	X
PCS (pain catastrophising)	X		X	X
Process measures				
CPAQ-8 (pain acceptance)	X		X	X
BADS-SF (behavioural activation for depression)	X		X	X
Other measures				
EQ-5D-5L (quality of life)	X		X	X
CEQ (credibility and expectations regarding treatments)	X		X	
CSRI (medication consumption and service receipt)	X			X
AET (negative effects of psychological treatments)			X	
PGIC and PSIC (impression of change)			X	
ACT-FM (fidelity measure)		X	X	
QBAS (fidelity measure)		X	X	
Pain Monitor app		X		
Physiological variables				
Immune-inflammatory markers	X		X	
HPA and vitamin D markers	X		X	
FKBP5 polymorphisms	X			

ACT-FM, Acceptance and Commitment Therapy Fidelity Measure; AET, Adverse Effects of Treatments checklist; BADS-SF, Behavioural Activation for Depression Scale (short form); BPI-IS, Brief Pain Inventory-Interference Scale; CEQ, Credibility/Expectancy Questionnaire; CIDI, Composite International Diagnostic Interview—depression section; CPAQ-8, Chronic Pain Acceptance Questionnaire (8-item version); CSRI, Client Service Receipt Inventory; CTQ-SF, Childhood Trauma Questionnaire–Short Form; DASS-21, Depression Anxiety Stress Scales-21; EQ-5D-5L, EuroQoL; HPA, hypothalamic–pituitary–adrenal; NRS, Numerical Pain Rating Scale; PCS, Pain Catastrophising Scale; PGIC, Patient Global Impression of Change; PHQ-9, Patient Health Questionnaire; PSIC, Pain Specific Impression of Change; QBAS, Quality of Behavioral Activation Scale.

and family history of medical/mental illness. Information regarding comorbidity with other diagnosed physical–psychiatric conditions and the type and dose of current drugs will be consulted in medical records.

The *Patient Health Questionnaire* (PHQ-9).[41 42] Each of the nine PHQ items corresponds to one of the DSM-IV Diagnostic Criterion A symptoms for major depressive disorder. Response options are 'not at all', 'several days', 'more than half the days' and 'nearly every day', scored as 0, 1, 2 and 3, respectively. In addition, the PHQ-9 has a functional impairment question (item 10) that asks how much the symptoms they endorse in the first nine items interfere with daily functioning. The questionnaire can be used algorithmically for the probable diagnosis of a depressive disorder, or as a continuous measure of scores ranging from 0 to 27, with cut-off points of 5, 10, 15 and 20, which set the levels of symptoms of depression as mild, moderate, moderately severe or severe. In the present work, if potential participants obtain a score ≥2 at item 9 (risk of suicide), additional assessment will be undertaken to explore the real risk of suicide. The telephone-administered version of the PHQ-9 showed adequate reliability (α=0.82),[43] therefore it seems highly recommendable for our telephone-based screening of concomitant depression symptomatology.

The *Composite International Diagnostic Interview—depression section* (CIDI V.3.0).[44] The CIDI is a fully structured diagnostic interview developed and validated by the WHO to be used with the general population by trained lay interviewers. The interview will be used to confirm the presence of major depression. The psychometric properties of the CIDI have been examined extensively and are highly sound.[44]

The *Childhood Trauma Questionnaire–Short Form* (CTQ-SF).[45] The CTQ-SF is a 28-item retrospective questionnaire designed to capture five dimensions of childhood maltreatment (each scale includes five items): physical abuse; emotional abuse; sexual abuse (SA); physical neglect and emotional neglect (EN). Additionally, there is a three-item minimisation/denial scale. Items are scored from 1 to 5 in order to reflect the frequency of maltreatment experiences ('never true' to 'very often true'). Higher scores indicate greater child abuse and neglect. The Spanish CTQ-SF obtained Cronbach's α values ranging from 0.66 for EN to 0.94 for SA.[46]

Primary outcome measure

The *Brief Pain Inventory-Interference Scale* (BPI-IS).[47] The BPI-IS is a seven-item self-report measure that assesses the extent to which pain interferes with general activity, walking, work outside and inside the home, sleep, mood, enjoyment of life and relationships, each rated on a 0 ('does not interfere') to 10 ('completely interferes') scale. Scoring is done by computing the arithmetic mean of all items, such that higher scores indicate greater pain interference. A reduction of 1 point on the BPI-IS is considered as a clinically meaningful change. The BPI-IS is highly recommended as an outcome in clinical trials of patients with chronic pain and the psychometric properties are well-established (α>0.80).[48]

Secondary outcome measures

The *Numeric Rating Scale* (NRS).[49] The NRS is a unidimensional measure of pain intensity mainly used for adults. The most used version is an 11-point numeric scale (a horizontal bar or line) with 0 representing 'no pain' and 10 representing 'worst pain imaginable'. Time frames vary between studies. In the present work, respondents will be asked to report average pain intensity over the last week.

The *Depression Anxiety Stress Scales-21* (DASS-21).[50] The DASS-21 is a self-report measure developed to differentiate between features of depression (low positive affect), anxiety (physical arousal) and stress (psychological tension/agitation) in clinical and non-clinical samples. In addition, the DASS has been validated in clinical chronic pain samples.[51] Responders are required to indicate the presence of a symptom over the previous week. Each item is scored from 0 ('did not apply to me at all over the last week') to 3 ('applied to me very much or most of the time over the past week'). There are seven items on each of the three subscales (Depression, Anxiety and Stress). Therefore, total scores in each scale can range from 0 to 21. Higher scores indicate more severe levels of depression, anxiety and stress. The Spanish version obtained adequate internal consistency (0.84, 0.70 and 0.82 for the depression, anxiety and stress scales, respectively).[52]

The *Pain Catastrophising Scale* (PCS).[53] The PCS will be used to assess the pain catastrophising thoughts. It is a 13-item measure that captures three dimensions: rumination over pain, magnification of pain and helplessness in the face of pain symptoms. Each item is answered on a rating scale of 5 points (0 = 'never', 4 = 'almost always'). Total scores on each scale can range from 0 to 52, with higher scores indicating more pain catastrophising thoughts. The Spanish PCS has shown good internal consistency (α=0.79) and test–retest reliability (r=0.84).[54]

Process measures

The *Chronic Pain Acceptance Questionnaire* (CPAQ-8).[55] The CPAQ-8 is a self-report measure reflecting engagement in important activities with pain and willingness to experience pain. The eight items are rated on a 7-point scale (0= 'never true', 6= 'always true'). Higher total scores reflect greater acceptance. The Spanish CPAQ-8 has adequate internal consistency, a Cronbach α values of 0.75.[56]

The *Behavioural Activation for Depression Scale—short form* (BADS-SF).[57 58] Behavioural activation is conceptualised as a key therapeutic process in BATD. The BADS-SF assesses this construct by means of a 9-item scale. Items are answered on a Likert scale of 7 points ranging from 0 ('not at all') to 6 ('completely'). Higher scores indicate greater behavioural activation in depressed individuals. The BADS-SF has shown adequate internal consistency (α=0.82).[57]

Other measures

The *EuroQoL* (version EQ-5D-5L).[59] The EQ-5D-5L is a health-related quality of life questionnaire that consists of two parts: in the first part, the individual's difficulties concerning mobility, self-care, pain/discomfort and anxiety/depression are evaluated; and in the second part, the current state of perceived health is assessed by a Visual Analogue Scale (VAS) ranging from 0 to 100. The EQ-5D-5L scores will be used to calculate the Quality-Adjusted Life Years (QALYs) during the follow-up period, adjusting the duration of time affected by the health outcome by the value of the utility.

The *Credibility/Expectancy Questionnaire* (CEQ).[60] The CEQ is a quick and easy to complete measure widely used to assess credibility and expectations regarding treatments. The CEQ contains six items: three of them focused on *therapy credibility* (the extent to which the treatment appears logical; the extent to which the treatment appears useful and the confidence with which the patient would recommend the treatment to a friend having the same problem) and three items assessing *expectations* (the extent to which the patient thinks an improvement will occur; the extent to which the patient feels that therapy will help him/her and the extent to which the patient feels an improvement will occur). The CEQ has demonstrated satisfactory psychometric properties.[60]

The *Client Service Receipt Inventory* (CSRI).[61] The CSRI will be used to collect retrospective data on medication consumption and service receipt. Regarding medication intake, patients are asked to bring their daily medication prescriptions and the following information for pain-related drugs (ie, analgesics, anti-inflammatories, opioids, muscle relaxants, antidepressants) is recorded: the name of the drug, the dosage, the total number of prescription days and the daily dosage consumed. Concerning service receipt, patients are asked about the total visits to accident and emergency services, the total number of general inpatient hospital admissions, the number of diagnostic tests administered and the total visits to healthcare professionals for pain management, including family physicians, nurses, social workers, psychologists, psychiatrists, group psychotherapy and other community healthcare professionals, specifying in each case if these services were provided by the public or by the private sector. The CSRI will be administered on two occasions: at baseline and at 12-month follow-up, both referring to the previous 12 months. Medical records will be checked to verify the accuracy of the collected data.

Ad-hoc measure of *Adverse Effects of Treatments*. It was developed in a previous RCT[36] and will be used to check the presence of negative effects of ACT and BATD. The item reads as follows: *Have you experienced, during the course of the psychological treatment, any unwanted symptom that you think might be directly or indirectly associated with the psychological intervention?*

The *Patient Global Impression of Change* (PGIC) and the *Pain Specific Impression of Change* (PSIC).[62] Patient impression of change measures are frequently used as indicators of meaningful change in treatments for chronic pain. The most frequently used scale is a 7-point numerical scale (from 1= 'Much better' to 7= 'Much worse'). The PGIC is one item referred to the perception of global improvement, whereas the PSIC asks about the impression of change in more specific domains: physical and social functioning, work-related activities, mood and pain. These scales will be completed by the participants who are assigned to ACT and BATD.

The *Acceptance and Commitment Therapy Fidelity Measure* (ACT-FM).[63] The ACT-FM is a recently developed 25-item measure that captures four areas: therapist stance, open response style, aware response style and engaged response style (each split into ACT consistent and ACT inconsistent items, making eight sections in all). Items are rated on a 4-point scale from 0 ('behaviour never occurred') to 3 ('therapist consistently enacts this behaviour').

The *Quality of Behavioural Activation Scale* (QBAS).[64] The QBAS is a 14-item scale designed to assess ability in implementing behavioural activation. Items are rated using a 7-point Likert-type scale with higher scores indicating higher implementation quality (total score range 0–96). A score of 3 on each item corresponds to satisfactory skill in implementing the BA component delineated by that item. Preliminary psychometric analysis of this instrument yielded adequate inter-rater reliability (intraclass correlation coefficient=0.72).

Ecological momentary assessment (EMA)

Pain severity and other pain-related variables included in the study (eg, mood symptoms and health-related quality of life, to name some examples) can fluctuate during the day and across days depending on many factors, such as environmental stressors. Additionally, retrospective evaluation is known to be susceptible to memory bias.[65] Retrospective evaluation can lead to overestimation of the symptomatology, which can be avoided by frequent evaluations of the present symptomatology. Moreover, the prospective and repeated evaluation over time substantially improves the accuracy, reliability and quality of research.[66] While EMA has been difficult for decades due to the problems associated with paper diaries, the availability of smartphones and the explosion of apps is making EMA easiest than ever.[67] There is growing evidence indicating that well-designed smartphone can be very easy to use and well accepted even in relatively old pain populations, and compliance rates with daily assessment have been as high as 75%.[66] In the present study, we will use the Monitor del Dolor (Pain Monitor) app, which has been recently validated in an empirical study[68] that assessed a number of biopsychosocial constructs twice a day during 4 weeks. In the present work, we will assess daily (twice a day: once in the morning and once in the evening, at convenient times) the items listed in table 4 during the 8-week treatment period.

Table 4 List of items administered via pain monitor app

Items	Morning	Evening
Pain intensity	X	X
Fatigue	X	X
Perceived control over pain	X	X
Openness to thoughts and feelings	X	X
Focused in the present moment	X	X
Guided by goals and values	X	X
Perceived competence	X	X
Activity level	X	X
Perceived stress	X	X
Perceived social support	X	X
Rumination	X	X
Magnification	X	X
Helplessness	X	X
Sleep disturbance	X	
Interference with leisure activities	X	X
Interference with work-related activities	X	X
Rescue medications	X	X

The Pain Monitor app informs patients automatically when to respond (by default, at 11 AM and 7 PM) using a push notification system, but patients can change the assessment times with a flexibility of 2 hours from given times. Collected data are stored on a secure server at the Jaume I University, Spain. The app and the data are stored on different servers with different domain names and connected locally only (the server containing the data does not have Internet access).[69]

Physiological variables

Immune-inflammatory markers. After drawing the blood, it will be allowed to coagulate for a minimum of 30 min at room temperature and then centrifuged for 10 min at 1000 g. The resulting serum will be stored at −80°C during the same morning of extraction until it is ready to be analysed. All samples (pre and post) will be analysed in a single analytical batch to reduce inter-assay variability (approx. 15%). The serum levels of cytokines IL-6, CXCL-8, IL-10, TNF-α, IL-1β and high-sensitivity C-reactive protein will be evaluated. For the quantification of the cytokines, the Milliplex reagents from the company MerckMillipore will be used and analysed using a Luminex platform. The high sensitivity multiplex kit will be used: Human High Sensitivity T Cell, catalogue number: HSTCMAG-28SPMX11 adapted to the aforementioned cytokines. The hs-PCR will be quantified using turbidimetry in an Olympus AU5400 auto-analyser.

Hair cortisol and cortisone, blood cortisol, CBG and vitamin D. Hair samples will be obtained from the middle-lower back area of the head as it is less exposed to environmental conditions such as sunlight, which affect the hormone levels in hair and as close as possible to the scalp. No products such as gels, lacquers or softeners will be used during the 3 days prior to obtaining the sample. A strand about 10 mm thick from the posterior vertex will be taken, packed in foil to avoid light impact and stored at room temperature. For the hormones determination only the 1 cm of hair closest to the scalp will be analysed. The extraction of hormones will be done from pre–post samples in the Nutrition and Obesity Laboratory of the Biochemistry and Molecular Medicine Department (University of Barcelona, UB), as they are obtained. The protocol consists, after hair samples weighing, of a previous wash with 5 mL of isopropanol to remove accumulated dirt and sweat, detergent residue or cosmetic products. Then, hair samples are dried at 37°C and minced. Cortisol and cortisone are extracted in 2 mL liquid chromatography with tandem mass spectrometry (LC–MS) grade methanol and stirring overnight at room temperature in the presence of deuterated Cortisol-d4 and Cortisone-d8 (Sigma Aldrich solution C-113 and 900170). The methanol is transferred to test tubes and evaporated in a dry bath at 50°C under a stream of N_2. The dried tubes are stored at −20°C until the quantification of cortisol and cortisone by LC-MS/MS at the Scientific and Technological Centres of the UB (CCiTUB). The levels of vitamin D and cortisol in serum will be determined by ELISA (DRG EIA-5396, EIA-1887R and EIA-3647) and CBG by RIA125I (IBL KIP1809) in a radioactive facility situated at the UB.

Polymorphisms in the FKBP5 gene. A blood sample of 4 mL will be collected in a vial with EDTA anticoagulant (BD Vacutainer; BD, NJ, USA). Specifically, the analysis of the genetic variants of the FKBP5 gene will be carried out in the Molecular Genetics Laboratory of the Anthropology Unit (UB). The samples will be coded, preserved and the DNA will be extracted with the Real Extraction DNA kit (Durviz S.L.U., Valencia, Spain). Quality of the DNA will be tested using the Nanodrop D1000 (Thermoscientific, Wilmington, DE). The genotyping of the five proposed SNP polymorphisms in the *FKBP5* gene will be carried out using TaqMan 5′ exonuclease assay (Applied Biosystems) technology at the Scientific and Technological Centres of the UB (CCiTUB): rs3800373 (SNP1), rs9296158 (SNP2), rs1360780 (SNP3), rs9470080 (SNP4) and rs4713916 (SNP5). The PCR reaction will be carried out on the ABI PRISM 7900HT instrument thermal cycler and genotype analysis will be carried out using SDS V.2.1 software (Applied Biosystems). For accuracy of genotyping, 15% of the samples, randomly selected, will be genotyped twice. Finally, the estimation of haplotypes will be conducted in order to increase the power to detect genetic associations.[69] Linkage disequilibrium between the five polymorphisms in the *FKBP5* gene will be examined by pair-wise comparisons of r2 and D' using Haploview V.4.2.[70] Estimation of *FKBP5* haplotype combination per subject will be conducted using a Bayesian approach implemented with PHASE software.[71]

Statistical analysis

The main analysis will compare the effect of the treatments on the primary outcome (pain interference at 12 months follow-up). All data analyses will be carried out

following an intention-to-treat (ITT) principle, that is, regardless of protocol adherence. Then, we will compute analysis of the primary outcome post-treatment and analysis of the secondary and treatment process outcomes at post-treatment and at 12-month follow-up. The analyses will be replicated from a per-protocol approach. Multi-level, linear mixed models will be created using the restricted maximum likelihood method for the estimation of parameters. The effect sizes will be calculated according to Cohen's *d*. No interim analysis is planned for this RCT. A 5% significance level will be used in all two-tailed tests, applying the Benjamini-Hochberg correction for multiple comparisons (to reduce the risk of false positives). For these analyses, we will use SPSS V.24.0.

To examine whether the effects of ACT and BATD in addition to usual care on primary and secondary outcomes at 12-month follow-up are mediated through pre–post changes in pain acceptance (CPAQ-8), and behaviour activation (BADS-SF), respectively, we will calculate pre–post changes in the total scores of the CPAQ-8 and the BADS-SF and pre-follow-up change scores in the primary and secondary outcomes. Then, bivariate Pearson correlations will be computed between the pre–post change in the process variables and the pre-follow-up change in the outcomes to detect potential significant relationships. Finally, we will explore the direct and indirect associations between the treatment condition (TAU+ACT vs TAU and TAU +BATD vs TAU as independent variable), CPAQ-8 and BADS-SF (mediators), and primary and secondary outcomes (dependent variables) using path analyses. The direct paths between the treatment condition and clinical outcomes and the indirect effect path through CPAQ-8, and BADS-SF will be tested in all models. Regression coefficients (B) of bias-corrected bootstrapped indirect effects will be calculated as well as their SEs and 95% CIs. Parameters of indirect effects are considered statistically significant when the 95% CI does not include 0. The MPlus V.7.4 will be used to compute the mediation models.

Regarding analyses of the EMA data, Group (TAU+ACT vs TAU+BATD vs TAU), Time (each of the EMA measurement points; up to two assessments per day × 60 days) and the Group × Time interaction will be the primary fixed effects of interest.

Regarding the economic evaluation, when the cost-utility of two or more therapeutic options is compared, it is necessary to calculate the relationship between the costs of each treatment and its consequences in the form of QALYs, a measure designed for assessing both quantity of life (years) and health-related quality of life (ie, a year lived with the maximum quality of life would be transformed into 1 QALY; a year lived with half the maximum quality of life would be transformed into 1/2 QALY). This relative value will be called the incremental cost-utility ratio (ICUR), and it will express the relationship between the costs and the effects of one option compared with another. The QALYs obtained in the 12 months after the start of the treatments will be calculated by the area under the curve.

The direct costs will be calculated by adding together the costs derived from the medication and the use of the health services. The cost of medications will be calculated by multiplying the price per milligram by the total daily dose consumed (in milligrams) and the number of days that the treatment is received. The cost arising from the use of the health services (primary care, specialist and accident and emergency consultations and hospital admissions) will be obtained from the eSalud database (http://www.oblikue.com/en/esalud.html). The indirect costs will be calculated based on the days off work, which will be multiplied by the official minimum wage during the study period. The effect of the treatments will be estimated using ordinary least squares multivariate regression, adjusting for the baseline differences between groups. In order to manage uncertainty in the sampling distribution of the ICUR, non-parametric bootstrapping will be applied, with 1000 replications in each comparison. Cost-utility analyses will be conducted with STATA V.16.0.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination of our research.

ETHICS AND DISSEMINATION

All procedures performed in this study will be in accordance with the 1964 Helsinki declaration and its last amendments (seventh revision, adopted by the 64th World Medical Association General Assembly, Fortaleza, Brazil). Signed informed consent will be obtained from all patients once they have been informed of the study procedures, potential risks and their right to withdraw at any time from the RCT. The FSJD Ethics Committee Board evaluated and approved the study protocol in September 2019 (PIC-178-19). The Hospital del Mar Ethics Committee Board evaluated and approved the study protocol in November 2019 (2019/8866/I). Only the principal investigator (JVL) will have full access to the final trial data set.

Once the RCT is completed, we will publish our results in international peer-reviewed biomedical journals and present them at national and international conferences. In addition, we will send participating patients a short report of our findings. A copy of the report will also be sent to Institute of Health Carlos III (main funding body). The principal investigator will organise an end-of-study knowledge translation seminar. The main objective of this activity will be to share the study findings with stakeholders in order to discuss how to maximise uptake of the findings in patient treatment and clinical practice, and to determine future research directions.

DISCUSSION

The present manuscript describes the design and protocol of an RCT that aims to assess the efficacy, cost-utility and physiological effects of adding ACT or BATD to TAU for the management of CLBP and moderate to severe levels of depressive symptoms. If the results are strong enough in terms of cost-utility, in one or both of the evaluated treatments (ACT and BATD), they could be considered for inclusion in the public healthcare system to treat patients with CLBP and depression, and could be used to treat similar conditions if such general applicability is demonstrated. The fact that these treatments are performed in groups can make them more cost-effective, and therefore of interest for health managers.[72] Additionally, if the results are positive, these treatments could also be tested in similar chronic conditions (eg, fibromyalgia, irritable bowel syndrome, or chronic fatigue syndrome) that also frequently present with comorbid depression symptoms.

This study has some strengths that should be highlighted. The inclusion of a large sample and the inclusion of a comprehensive set of measures will allow us to explore important pain-related outcomes and treatment mediators. Our study will both focus on the clinical effects of ACT and BATD as add-on treatments in the long-term, and also on the psychological constructs and physiological variables that may be involved in the changes experienced by patients after treatment. On the whole, our study explores genetic, neuroendocrine (HPA axis) and immune-inflammatory (cytokines) pathways with a combination of technologies which may lead to a characterisation of biochemical markers and targets relevant to increase our understanding of both chronic pain and depression, new therapeutic interventions to manage these disorders, and a better prediction of treatment results based on individual variations of these biomarkers in the line of personalised medicine. In addition, this study will use a smartphone app to monitor the treatments' effects ecologically, which is a novel approach into the pain literature exploring the effectiveness of psychological interventions.

It is important to mention that we will analyse five different polymorphisms in the *FKBP5* gene whose interest relies on its implication in HPA axis stress response regulating glucocorticoid receptor affinity and signalling. Previous gene-environment studies have found associations between the variability of this gene and early trauma with depression[73 74] and anxiety.[75] Based on these findings, our main aim is to explore, for the first time, the moderator role of the interaction between *FKBP5* gene polymorphisms and childhood trauma on the response to psychological treatments for chronic pain and depression.

There are some potential limitations that should be acknowledged. First, there may be a higher than expected dropout rate due to the length of the study (1 year). Second, there is a risk that not all recruited patients have a smartphone or that completion rates may be unsatisfactory, so EMA might not be possible or effective for all participants. Participants who do not engage will not be excluded, but the analyses will be limited to the classical assessments. Finally, we have to note the lack of blinding of patients and therapists, a typical bias in RCTs of psychological treatments.

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Contributors JVL, AF-S and JRC-A designed the major outlines of the study. PC-N, CS-R, AG-P, AC-C, AP-A, LA-R, LMMcC, FD'A, PE-R, BC-M, AM-P, OC-V, ME, MG, AR, AIC-V, MM, XB, SE, AS and AF-S contributed to the study design. PE-R, JRC-A, AM-P and OC-V will include patients in the study. JVL, CGF and FD'A carried out the sample size calculation. JPS-M wrote the first draft of the manuscript together with JVL, AF-S, JRC-A and CS-R. All authors read and approved the final version of the manuscript.

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