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Cost-effectiveness and cost-utility evaluation of the individual vs. group transdiagnostic psychological treatment for emotional disorders in Primary Care (PsicAP-Costs) V.2

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Abstract

The aim of this study is to compare, in cost-effectiveness and cost-utility terms, a brief transdiagnostic cognitive-behavioural therapy in two different modes, individual and group, with the treatment usually administered in primary care (TAU).

Participants between 18 and 65 years old and with, according to the pretreatment evaluation, mild to moderate emotional disorders will be randomly allocated to the three clusters. They will be assessed again immediately after treatment and 6 and 12 months later.

ClinicalTrials.gov: **NCT04847310**

Materials

Primary outcomes

- *Depressive symptoms: 9-item Patient Health Questionnaire (PHQ-9)*

The PHQ-9 (Kroenke et al., 2001) is the depression module of the PHQ (Díez-Quevedo et al., 2001; Spitzer et al., 1999), that scores the 9 DSM-IV depression criteria present in the last two weeks from 0 ("*not at all*") to 3 ("*nearly every day*"). A score of 10 is usually set as the cut-off point for major depression disorder (MDD): a score of 10-14 indicates minor depression, moderate MDD, or dysthymia; 15-19, moderately severe MDD; and 20-27, severe MDD. This tool has been tested in Spanish primary care centres (McDonald's ω = .89) (Muñoz-Navarro, Cano-Vindel, Medrano et al., 2017), finding 12 as the best cut point for MDD diagnosis (sensitivity of 84% and specificity of 78%) compared with 10 (sensitivity of 95% and specificity of 67%).

- *Anxiety symptoms: 7-item General Anxiety Disorder scale (GAD-7)*

The GAD-7 (Spitzer et al., 2006) assesses common anxiety symptoms in the last two weeks, scoring from 0 ("*not at all*") to 3 ("*nearly every day*"). Cut points of 5, 10, and 15 represent mild, moderate, and severe anxiety, respectively. The algorithm sets 8 as the cut point for GAD, however it has been found that a score of 10 is more optimal (Spitzer et al., 2006). We will use the version validated by García-Campayo et al. (2010), that was recently tested in primary care centres (Cronbach's α = .83) (Muñoz-Navarro, Cano-Vindel, Moriana et al., 2017), confirming the score of 10 as the best diagnostic criterion (sensitivity of 87% and specificity of 78%).

- *Panic symptoms: Patient Health Questionnaire-Panic Disorder (PHQ-PD)*

The PHQ-PD is the specific panic disorder module of the PHQ and scores each DSM-IV criterion as "yes" or "no" (Wittkampf et al., 2011). Muñoz-Navarro et al. (2016) tested it in Spanish primary care settings and modified the original algorithm to increase the sensitivity for PD diagnosis: the most optimal cut-off point for screening purposes was 5 (sensitivity of 77% and specificity of 72%).

- *Somatizations: Patient Health Questionnaire 15 items (PHQ-15)*

The PHQ-15 (Kroenke et al., 2002) is the somatization module of the PHQ and scores symptoms present in the past four weeks from 0 ("*not bothered at all*") to 2 ("*bothered a lot*"). It includes 13 somatic symptoms plus 2 from the PHQ-9 (sleeping problems and fatigue). Cut points 5, 10, and 15 represent low, medium, and high somatic symptom severity, respectively. For a probable somatization disorder diagnosis, it is necessary a score of 2 in three or more symptoms, (sensitivity of 78% and specificity of 71%) (van Ravesteijn et al., 2009). Furthermore, there must be an absence of a biological cause, since PHQ-15 does not distinguish between medically explained and unexplained symptoms (Kroenke et al., 2002). The PHQ-15 has been validated with Spanish psychiatric outpatients (α = .78) (Ros et al., 2010).

- *Eating disorders and alcohol abuse*

The PHQ also lets to measure the presence of other mental disorders. The Spanish version (Díez-Quevedo et al., 2001) detects eating disorders, such as bulimia nervosa or binge eating disorder, with a sensitivity of 92% and a specificity of 98%; and alcohol abuse with a sensitivity of 76% and a specificity of 99%. Affirmative answers to items 6a to 6c and 8 indicate bulimia nervosa; if item 8 were answered negatively (or unanswered), it would point out a binge eating disorder. An affirmative answer to any of the items 10a to 10e would indicate alcohol abuse. In any of these cases the patient would be interviewed by a clinical psychologist to confirm a possible diagnosis of eating, alcohol or personality disorder.

Secondary outcomes

- *Level of disability: Sheehan Disability Scale (SDS)*

The SDS (Sheehan et al., 1996) is a self-administered test that measures the subjective symptom-related impairment with five 11-point Likert items. The three first items rate key areas in the past month: work, social life/leisure activities, and family life/home responsibilities. It has two additional items to assess stress level and perceived social support in the past week. We will use the Spanish version developed by Bobes et al. (1999), that has shown good properties with primary care population (α = .83) (Luciano et al., 2010). One, four, and seven are the cut points for mild, moderate, and high disability, respectively. A total score of 25 or more indicates a general high disability, and the patient will be asked by a clinical psychologist to confirm: 'Are you on sick leave?', 'Can you do the housework?', and 'Can you engage socially?' (one question per area).

- *General quality of life: World Health Organization Quality of Life Instrument-Brief version (WHOQOL-BREF)*

Psychological, physical, social, and environmental domains will be assessed through the twenty-six 5-point Likert items of the WHOQOL-BREF (The WHOQOL Group, 1998b), the abbreviated version of the 100-item WHOQOL (WHOQOL-100) (The WHOQOL Group, 1998a). The more the participant scores, the better quality of life they have. The WHOQOL has been validated with Spanish population (Lucas-Carrasco, 2012; Rocha et al., 2012) and has shown good psychometric properties: $\alpha > .7$ in psychological, physical, and environmental domains, though social domain's internal consistency varies from .58 (Rocha et al., 2012) to .75 (Lucas-Carrasco, 2012).

- *Ruminative responses: Ruminative Responses Scale (RRS)*

The RRS (Nolen-Hoeksema & Morrow, 1991) was originally developed to measure the ruminative responses to depressed mood. It has been validated with Spanish population (Hervás, 2008), however, only the 5-item 'brooding' factor subscale (RRS-B) will be used in this trial (α = .79) (Muñoz-Navarro et al., 2021). The RRS-B scores from 1 ("*almost never*") to 4 ("*almost always*") how often the participant thinks as it is described in each item when they are discouraged, sad or depressed.

- *Worry: Penn State Worry Questionnaire (PSWQ)*

The PSWQ (Meyer et al., 1990) measures the pathological worry as an uncontrollable and general state (i.e., as a GAD feature). It has been validated in Spain (Sandín et al., 2009) and, in this study, it will be used an 8-item

abbreviated version (PSWQ-A) (Crittendon & Hopko, 2006) that has already showed good properties in primary care (α = .9) (Muñoz-Navarro et al., 2021). The PSWQ-A items rate how much worries affect the person from 1 ("*not at all typical of me*") to 5 ("*very typical of me*").

- *Attentional and interpretational biases: Inventory of Cognitive Activity in Anxiety Disorders (IACTA) and Questionnaire of Cognitive Distortions in Emotional Disorders (CDTE)*

The IACTA was originally developed by Cano-Vindel (2001). It includes subscales that assess distortions according to Eysenck's four-factor theory (Eysenck, 2000). The abbreviated panic version (IACTA-PB; α = .87) (Muñoz-Navarro et al., 2021) will be used to measure attentional biases. It specifically scores from 0 ("*almost never*") to 4 ("*almost always*") how often the participant has certain cognitive distortions.

The CDTE (The PsicAP Group, unpublished) scores from 0 ("*almost never*") to 4 ("*almost always*") the frequency of certain cognitive biases in the main EDs (MDD, GAD, PD, and somatization disorder). It includes 16 items that measure the presence of four factors: sustained attention bias (α = .96), divided attention bias (α = .95), magnification interpretational bias (α = .94), and catastrophization interpretational bias (α = .96), with high levels of discriminant validity among the four EDs (ROC values > .8).

- *Emotion regulation strategies: Cognitive Emotion Regulation Questionnaire (CERQ)*

The CERQ-36 (Garnefski et al., 2001) was developed for measuring the specific cognitive emotion regulation strategies that a person uses to face a stressful event. It scores from 1 ("*almost never*") to 5 ("*almost always*") how often the participant thinks as described. The CERQ has been validated with Spanish population (Domínguez-Sánchez et al., 2013) and the 27-item shortened version (Holgado-Tello et al., 2018) will be used (α values range from .72 ['acceptance'] to .88 ['positive refocus']).

- *Metacognitive beliefs: Metacognitions Questionnaire 30 items (MCQ-30)*

The MCQ-30 (Wells & Cartwright-Hatton, 2004) is a short form of the original MCQ (Cartwright-Hatton & Wells, 1997), which measures the beliefs about the own thinking processes. It has been validated with Spanish population (Ramos-Cejudo et al., 2013) and, in the current trial, only the 6-item 'negative beliefs' (about uncontrollability/danger) subscale (MCQ-NB; α = .82) will be used (Muñoz-Navarro et al., 2021). It scores from 1 ("*totally disagree*") to 4 ("*totally agree*") how the patient agrees with the sentences written.

- *Sociodemographic and medical data, and treatment satisfaction*

An *ad hoc* questionnaire will be used to collect sociodemographic (gender, age, civil status, educative level, employment situation, and income level) and ED-related medical data (public and private health care consultations, accidents, medical tests, and sick leaves in the past 3 months; psychotropic drugs or other medication, and their posology), and it includes an additional question about treatment satisfaction (only at post-treatment and follow-ups). Medical records will be also consulted to complete the information (for privacy reasons, only strictly necessary data will be collected).

- *Cost and utility data*

The medical data collected will be used for cost calculations too. In addition, cost-utility will be measured through the European Quality of Life Scale (EuroQoL, EQ) (The EuroQol Group, 1990). The Spanish version of the 5-domain, 5-level EuroQol (EQ-5D-5L) (Badia et al., 1999; van Reenen et al., 2019) will be used to calculate the quality-adjusted life years (QALYs). The EQ-5D-5L measures five domains of health-related quality of life (mobility, self-care, daily activities, pain/unease, and anxiety/depression) through 5 severity levels ("*no problems*", "*slight problems*", "*moderate problems*", "*severe problems*", and "*extreme problems*"), being able to stablish up to 3125 different health states, each of which can be represented through an index value that reflects the health state quality contextualized in the person's country/region. It also includes a visual analogue scale (VAS) that scores from 0 to 100 the current subjective, general health state.

Other pre-specified outcomes

- *Presence of emotional disorder (inclusion criterion): Patient Health Questionnaire 4 items (PHQ-4)*

The PHQ-4 (Kroenke et al., 2009) will be used for the recruitment phase. The PHQ-4 gathers the two items from the PHQ-2 and the two from the GAD-2 (short versions of the PHQ-9 and GAD-7, respectively). It has been studied with Spanish primary care population (Spearman-Brown's ρ[PHQ-4] = .72; ρ[PHQ-2] = .86; ρ[GAD-2] = .76) (Cano-Vindel et al., 2018): a score greater than or equal to 3 would indicate a need of additional assessment (PHQ-2: sensitivity of 90%, specificity of 61%; GAD-2: sensitivity of 88%, specificity of 61%). It may be an extremely useful tool, as it helps to accelerate the screening process, however, it has been suggested that both PHQ-2 and GAD-2 sum scores should be regarded separately in primary care samples (Cano-Vindel et al., 2018). The first item from the PHQ-PD has been added to screen panic disorder.

- *Presence of severe mental disorders (exclusion criterion)*

In the case of scoring as a severe ED (depressive or anxiety disorder) or other mental illness in the PHQ, or when the diagnosis is not clear, the patient will undergo a second evaluation with a gold-standard tool. The Structured Clinical Interview for DSM Axis-I Disorders (SCID-I) (First et al., 1999) will be used to assess panic and depression disorders, whereas the Composite International Diagnostic Interview (CIDI) (WHO's Mental Health Division, 1997) will be used for GAD (since the former may not be adequate as it only includes one item for GAD).

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Troubleshooting

RECRUITMENT AND FIRST ASSESSMENT

1 The recruitment will be accomplished in three different primary care settings of the province of Cordoba: the "Carlos Castilla del Pino" Health Centre, the "Levante Sur Dr. Manuel Barragán Solís" Health Centre, and the Community Mental Health Unit of Montilla. General practitioners (GPs) will invite the patients in whom they suspect a diagnosis of emotional disorder (ED) to participate in the study. Participants will be informed and asked for the written consent, and an assessor-investigator (the blinded party) will administer the instruments (see Materials).

Participants will be only adult (18-65 year-old) men and women who have mild or moderate EDs (i.e. depressive, anxiety and/or somatoform disorders) according to the PHQ subscales: the PHQ-4 for the screening, and the PHQ-9, the GAD-7, the PHQ-PD, and the PHQ-15 to determine the kind of disorder and the severity level. Those who do not have an ED and/or do have a severe mental illness, will be returned to their GPs. Participants with a recent, severe suicide attempt, or with a high level of impairment (according to the SDI) will be excluded as well.

The **sample size** needed would be 128.

Start date of the recruitment: September 2021.

INTERVENTION

2 Participants will be allocated, by a non-assessor investigator with a computer-generated randomization, to the three experimental groups (1:1:1 ratio):

- **Group brief transdiagnostic cognitive-behavioural therapy (group tCBT)**

An adaptation of the Unified Protocol for the Transdiagnostic Treatment of Emotional Disorders (UP) (Barlow et al., 2015) and the IAPT programme (Clark, 2018). It has been developed by Cano-Vindel (González-Blanch et al., 2018) and consists in seven 90-minute sessions, provided by a non-assessor clinical psychologist in 12-16 weeks, with 8-10 participants per group. Sessions are weekly or biweekly, reducing their frequency as the intervention advances. The activities and homework proposed are supported with materials such as theory documents, a CD for progressive muscle relaxation, self-recording sheets, and a therapy web (www.desordenesemocionales.es).

- **Individual brief transdiagnostic cognitive-behavioural therapy (individual tCBT)**

An adaption of the group therapy, with the same phases. However, since it is an individual intervention, it is more flexible than group one and its contents and duration can be personalized. This intervention consists of a minimum of 6 and a maximum of 8 sessions of 30-60 minutes, provided by a clinical psychologist not involved in the assessments.

- **Treatment as usual (TAU)**

Participants in this group will be provided the common primary care treatment by the GP, in a face-to-face consultation that seldom exceeds 10 minutes. TAU usually consists in pharmacological treatment prescribed by the GP, however, it might also consist in practical advice or even non-treatment (Watts et al., 2015). The first consultation will count as part of the recruitment process and, if the patient accepts to participate in the trial, no therapeutic help will be provided to them until they are allocated. Once in the TAU intervention, if the practitioner recommended any psychological treatment as part of it (e.g., referral to specialized care), the participant would be excluded to avoid contamination between clusters. TAU has not a specific amount of sessions; it will finish when the GP considers the patient is recovered.

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SECOND ASSESSMENT AND FOLLOW-UPS

3 Instruments will be administered again after each intervention is finished. They will be administered again 6 and 12 months later in order to assess if the potential changes remain over time.

ANALYSES

4 **ANALYSIS OF CLINICAL EFFECTIVENESS**

Data analyses will be accomplished through the SPSS Statistics software. Effectiveness-related data will be analysed with both intention-to-treat and per protocol approaches. After homogeneity intra- and inter-groups is checked, changes over time (baseline, post-intervention, and follow-ups) in primary and secondary outcomes will be analysed through linear mixed models (LMM). Likewise, effect sizes (Cohen's *d*) will be calculated, as well as their accuracy considering the number of treatment sessions received. Moreover, it will be estimated the percentage of patients in each cluster who experience a 50% decrease in the number of clinical symptoms and scores by one standard deviation, as well as the percentage of cases with a probable ED before and after receiving treatment (according to cut-off criteria). Therapeutic success criteria will be the obtaining of post-intervention means significantly lower ($p \leq .05$) and medium/large effect sizes significantly greater than the control's, especially in the ED scores. Clusters will be also compared regarding impairment, quality of life, emotion regulation biases, and satisfaction with the treatment.

COST ANALYSIS

Cost-related data will be collected through the medical records and *ad hoc* questionnaires, from 3 months prior to inclusion in the study to 12 months after the intervention has finished. Direct costs will be calculated by adding the ED-related costs due to medication use (antidepressants, anxiolytics, hypnotics, and sedatives), medical tests and other health services, and health personnel. Medication costs will be calculated by multiplying the price per milligram (€/mg) according to the Vademecum International (**www.vademecum.es**) by the daily dose (mg) and the number of days of drug treatment. Cost data related to medical tests and use of health services will be obtained through the fee information published in the Andalusian Health Service's official web. Since a group psychotherapy session has not a specific tariff, it will be considered as a GP consultation without medical tests as GPs and clinical psychologists have similar base salaries. Indirect costs will be calculated by multiplying the days of ED-related sick leave from work by the daily minimum salary at the moment, and it will be also taken into

account if it is necessary a replacement worker. Total costs will be obtained summing both direct and indirect costs.

ANALYSES OF COST-EFFECTIVENESS AND COST-UTILITY

On the one hand, cost-effectiveness analysis will be accomplished by calculating the incremental cost-effectiveness ratios (ICERs). However, cost-effectiveness analyses may be questioned, since they rate the more appropriate intervention based only on the clinical perspective. On the other hand, cost-utility analyses use the intervention health-related utilities, subjectively rated by participants. Therefore, they depend on a social perspective, being the participants who express their preferences based on the value they assign to their health status. The EQ-5D-5L will be used to calculate those utilities as QALYs, and the latter to obtain the incremental cost-utility ratios (ICURs). Since follow-ups will not last more than 12 months post-intervention, neither costs nor results will be subject to discount. The bootstrapping method (a resampling method) will be used to obtain more accurate ICERs and ICURs. Missing data will be analysed through Student's t and χ^2 tests regarding ED severity level, sex, and age; this will allow us to know if missing data due to dropout are related to chance or not. Finally, a sensitivity analysis will be done to test the robustness of cost-effectiveness and cost-utility results.

Expected result

Hypothesis 1: The individual treatment will be generally as effective as the group one.
Hypothesis 2: The TAU will be the least effective.
Hypothesis 3: The group therapy will get the best results in terms of cost-effectiveness and cost-utility.
Hypothesis 4: The TAU will get the worst cost-effectiveness and cost-utility results.
Hypothesis 5: The same results will be found across the follow-up assessments.