1 **Abstract**

2 The purpose of this study was to assess the effect of a tailored cognitive-behavioral

3 therapy (CBT) for depression and anxiety symptoms in Mexican terminal cancer

4 patients. A non-concurrent multiple baseline design across individuals was used. Nine

5 patients participated in the study, and they received four to six therapy sessions. The

6 effect size of the intervention range (NAP and Tau indexes) in the nine patients

7 indicated that the intervention had from weak to moderate impact for anxiety and

8 depression symptoms in this population. Similarly, the overall standardized mean

9 difference was also moderate, with a reduction of 0.54 and 0.76 standard deviations in

10 depression and anxiety symptoms, respectively. This study provides initial evidence

11 supporting the positive effect of CBT for patients with terminal cancer and with mood

12 problems when facing their impending death.

13 *Keywords:* Terminal Cancer, depression, anxiety, cognitive behavioral therapy, single-

14 case experimental design

15 **Introduction**

16   Depression and anxiety are the most frequently reported emotional problems by

17 advanced cancer patients. Studies show that 10% to 48% of these patients are anxious

18 (Mitchell et al., 2011; Spencer, Nilsson, Wright, Pirl, & Prigerson, 2010), and 9% to

19 40% are depressed (Hotopf, Chidgey, Addington-Hallm, & Ly, 2002; Teunissen et al.,

20 2007). Patients with anxiety, depression, or a combination of both, tend to report greater

21 frequency and intensity of physical symptoms compared to patients who do not display

22 these emotional problems (Delgado-Guay, Parsons, Li, Palmer, & Bruera, 2009).

23   Treatments such as antidepressants, anxiolytics, benzodiazepines, in

24 combination with psychotherapy are usually considered first-line interventions for

25 anxiety and depression. Current evidence-based information suggests that cognitive

26 behavioral therapy (CBT) should be considered to treat anxiety and depression in

27 advanced cancer patients (Okuyama, Akechi, Mackenzie, & Furukawa, 2017; Rayner,

28 Price, Hotopf, & Higginson, 2011; Traeger, Greer, Fernandez-Robles, Temel, & Pirl,

29 2012).

30   Given the cognitive and physical decline in terminal cancer patients, it is

31 noteworthy that research in this field had to adapt components of CBT to the needs and

32 characteristics of these patients. The number of sessions with this population tends to be

33 shorter (4 to 8 sessions) than the number of sessions in other settings (Anderson,

34 Watson, & Davidson, 2008; Savard et al., 2006). Investigators have also tailored certain

35 components of CBT to address realistic but intrusive and distressing thoughts about

36 symptoms, functionality, and death (Greer et al., 2012; Greer, Park, Prigerson, &

37 Safren, 2010). In addition to traditional face-to-face therapy, researchers have assessed

38 other modalities of intervention delivery, such as group therapy (Edelman, Bell, &

39 Kidman, 1999) and home-based therapy (Moorey et al., 2009) with positive effects in

40 depression and anxiety symptoms respectively.

41   Despite efforts to adapt CBT to terminal cancer patients, the special conditions

42 of patients living in developing countries such as Mexico differ from patients who have

43 participated in CBT and terminal cancer studies elsewhere. Such differences may affect

44 the ecological validity and cultural sensitivity of those interventions for Hispanic

45 populations (Bernal, Bonilla, & Bellido, 1995; Okuyama et al., 2017). Late referral to

46 palliative care services is very common in developing countries, and it leads to 1) short

47 life expectancy in palliative care patients (an average of three months); and 2) more

48 physical symptoms experienced by terminally ill patients. Additionally, salient factors

49 specific to Mexican or Hispanic populations ought to be considered when designing or

50 adapting a therapy: 1) at least 55.3 million Mexicans live in poverty or extreme poverty,

51   so they lack the necessary income to satisfy basic health and transportation needs; and

52   2) in Mexico it is common that not only nuclear family members, but also extended

53   family, actively participate in a patient's care and decision-making (Consejo Nacional

54   de Evaluación de la Política de Desarrollo Social, [National Council for the Evaluation

55   of Social Development Policy], 2015; Covarrubias-Gómez, Hernández-Martínez, Ruiz-

56   Ramírez, & López Collada-Estrada, 2014; De Vos, Solís, & Montes de Oca, 2004).

57   The difficult conditions that Mexican terminal cancer patients encounter and the

58   lack of empirical evidence make it necessary to assess CBT strategies that are specific

59   to this population. Therefore, it is pertinent to develop cultural adaptations of CBT

60   relevant to the conditions of this population. For example, interventions would ideally

61   include a fewer number of sessions, emphasize psychological strategies for symptom

62   control, use home-based therapy to avoid patients' fatigue due to transportation or lack

63   of financial resources, and allow flexibility to involve one or more family members.

64   In addition to the clinical adaptations, Penrod & Morrison (2004) have

65   highlighted the need to increase research in this area with particular attention to the

66   "challenges for palliative care research." Conducting research in patients with

67   advanced cancer who are close to death involves numerous ethical, clinical and

68   methodological challenges. Researchers in this field should be focused on application of

69   methodology that is adapted to the patient's context and needs. Although randomized

70   controlled trials (RCT) are the "gold standard" for conducting clinical research in the

71   current evidence-based practice, when RCT are applied in palliative care settings

72   several limitations have been documented such as unethical issues for withholding the

73   treatment from the control group; the lack of feasibility to employ RCT for every

74   palliative care clinical question and patient population; poor patient accrual for the

75   studies; and the aim of RCT to demonstrate efficacy but not necessarily effectiveness.

76   Studies are therefore needed to implement novel and realistic systems for interventions

77   targeting people with advanced cancer, given the difficulty of conducting clinical trials

78   in this population (Okuyama et al., 2017).

79   The use of single-case experimental design (SCED) or N-of-1 trials as they are

80   formally known in medicine (Tate et al., 2016) could be an alternative approach to

81   advance in the research of available interventions within the field for patients with

82   terminally ill cancer in palliative care settings. Recently, the importance of conducting

83   this kind of research has been highlighted, because SCEDs (a) allow rigorous internally

84   valid scientific investigation of the effectiveness of a particular treatment for an

85   individual (Lobo, Moeyaert, Cunha, & Babik, 2017), rather than the population mean

86   (Normand, 2016); (b) help to assess early effects (Graham, Karmarkar, & Ottenbacher,

87   2012); (c) are less expensive and more feasible than other experimental approaches; (d)

88   can complement information retrieved from other experimental designs (Shadish,

89   Hedges, Horner, & Odom, 2015); (e) favor the extrapolation of results on the basis of

90   the comparison between the features of the client, behavior, and setting for which

91   effectiveness has been demonstrated and the features of the situation any given

92   practitioner is facing (Schlosser, 2009); and (f) when several studies are available on the

93   same intervention for the same type of problem the results may be pooled via meta-

94   analyses (Jenson, Clark, Kircher, & Kristjansson, 2007; Punja et al., 2016).

95   Given the above, using the SCED can be an appropriate option to conduct

96   psychological research with advanced cancer patients (Lévesque, Savard, Simard,

97   Gauthier, & Ivers, 2004). Even though an adapted CBT seems to be a promising

98   approach for those with considerable morbidity, no empirical data exist to discern

99   whether this mode of therapy is effective in Mexican terminal cancer patients.

100   Therefore, the aim of this study was to assess the effect of a tailored CBT for depression

101   and anxiety symptoms in Mexican terminal cancer patients. A secondary aim was to

102   evaluate the effect of the intervention on the leisure activities self-report and on the type

103   of thoughts related to the patient's advanced cancer, as well as to their perception of the

104   main benefits and harm they experienced throughout the therapy.

Method

Design

107   A non-concurrent A-B multiple baseline design across individuals was used.

108   Multiple-baseline design is highly recommended because "the effects are demonstrated

109   by introducing the intervention to different baselines at different points in time. If each

110   baseline changes when the intervention is introduced, the effects can be attributed to the

111   intervention rather than to extraneous events" (Kazdin, 2011, p. 144). Given the short

112   life expectancy of participants, it was decided to use three cohorts of three patients in

113   each cohort in order to avoid prolonged baseline records that could lead to a patient's

114   death without treatment and also in order to generate at least three replications of the

115   treatment intervention. Phase "A" consisted of the baseline, which included an

116   evaluation using the Hospital Anxiety and Depression Scale (HADS). The duration of

117   the baselines was two, three or four assessments during this phase. For each cohort,

118   each of the previously specified baseline lengths occurred once. Simple computerized

119   randomization was used to determine the time at which phase change occurs for each

120   participant. During this phase, patients and primary caregivers were trained to fill out

121   their activities, thoughts and mood diary daily, and their HADS instruments weekly.

122   Phase "B" consisted of intervention and post-assessment. During this phase,

123   patients completed their activities, thoughts and mood diary and anxiety and depression

124   mood records; they also completed the HADS weekly until their health permitted, or for

125   up to one month after completing the treatment.

Participants

127   The following inclusion criteria were required for study participation: patients at

128   least 18 years of age; diagnosis of terminal cancer (stage IV cancer with no curative

129   treatment and referred to palliative care); and clinically significant anxiety and/or

130   depression symptoms according to the HADS scores (depression ≥ 7; anxiety ≥ 8). Three

131   participants had depression symptoms only, and six had depression and anxiety

132   symptoms. The exclusion criteria included: patients with stage I, II, and III cancer;

133   patients with cognitive impairment or delirium; and patients with low functionality

134   levels which prevented them from taking therapy (functionality was measured using the

135   Palliative Performance Scale [PPS] $\leq 30\%$; see the instruments description). 117

136   patients with terminal cancer were assessed during the fourteen months that this

137   investigation lasted, but 108 patients (92%) were not in adequate conditions to

138   participate in this research (90 were extremely ill to participate [PPS ≤ 30]; 4 developed

139   delirium; 5 had subthreshold of anxiety or depression; and 9 had other reasons). Nine

140   terminal cancer patients from the Pain and Palliative Care Department of a General

141   Hospital in Mexico City participated in this study. Six women and three men were

142   included, with an average age of 63.3 years (range: 40-83 years). The average score for

143   the Palliative Performance Scale (PPS, see description below) was 64 (range: 40-90);

144   and the mean survival was 119 days. Pancreatic, liver and cervical terminal cancers

145   were common in these participants. Additional demographics are displayed in Table 1.

146

147   [TABLE 1]

Setting and Approval

149   CBT was delivered at patients' homes (living room or patient's bedroom), which

150   were located in Mexico City's metropolitan area. The shortest travel time by taxi from

151   the hospital to a patient's home and back was 25 minutes, and the longest was 160

152   minutes. All patients signed an informed consent form before participating in the study.

153   Permission for the research was granted by the "Hospital General Dr. Manuel Gea

154   González" in Mexico City with registration number 47-01-2014.

155   **Instruments**

156   Clinical medical records of patients were used to verify health and

157   sociodemographic information, as well as to obtain data on their functional status and

158   physical symptoms. An exhaustive review was performed in order to find studies

159   reporting validity, reliability, specificity and sensitivity of instruments to assess anxiety

160   and depression in oncologic and terminal patients (Mitchell, Meader & Symonds, 2010;

161   Vodermaier, Linden, & Siu, 2009). Until now there is no a single method specifically

162   designed to accomplish those purposes, so it is recommended to use a two-item

163   interview (initial assessment), combined with self-reported assessment and

164   behavioral/thoughts records. All of them are described below.

165   **Instruments used for screening purposes**

166   **Two-question interview**. Two questions derived from the Edmonton Symptom

167   Assessment System (ESAS) were used as an initial screening of severity for anxiety and

168   depression ("Are you anxious?" "Are you depressed?"). We scored ESAS items through

169   a numeric scale ranging from 0 (absence of the symptom) to 10 (worst possible severity;

170   Hannon et al., 2015). If patients reported anxiety or depression (ESAS > 1), HADS

171   scales were applied. This assessment method has proven to be valid and reliable for the

172   Spanish-speaking population ($\alpha = 0.75$-0.86), and it has further shown to be a useful

173   tool to assess the symptoms of the palliative population in Mexico (Carvajal, Hribernik,

174   Duarte, Sanz-Rubiales, & Centeno, 2013; Covarrubias-Gómez et al., 2014).

175   **Palliative Performance Scale (PPS).** This scale is used to evaluate the

176   palliative patient's functionality level. Palliative care physicians completed the PPS

177   scale to identify the patient's level of functionality in five domains: ambulation,

178   activity, and evidence of disease; self-care and intake; and level of consciousness. For

179   each domain, the physician establishes the value that best represents the patient's ability

180   and health. This value ranges between 100% (patient with no evidence of disease) and

181   0% (patient who has died). If patients showed a PPS lower than 30%, they were not

182   included in the study because their PPS score reflected fewer survival days (Lau et al.,

183   2009). The PPS scale has shown to be valid and reliable for the Spanish-speaking

184   population (test-retest reliability was 0.89) and has proven to be a useful tool to assess

185   the functionality of the palliative population in Mexico (Barallat et al., 2017;

186   Covarrubias-Gómez et al., 2014).

187   **Confusion and delirium assessment**. Two self-reported scales adapted and

188   validated for Spanish-speaking populations were employed to identify cognitive

189   disorders associated with chronic diseases (Lobo et al., 1999) and delirium (Wei,

190   Fearing, Sternberg, & Inouye, 2008). If patients had cognitive problems or delirium,

191   they were not included in the study.

192   **Instruments used to measure the study variables**

193   **Hospital Anxiety and Depression Scale (HADS)**. HADS is a widely-used

194   scale to measure anxious or depressed mood in medical patients, including those

195   diagnosed with cancer (Zigmond & Snaith, 1983). The scale includes 14 Likert-type

196   questions (seven of the items relate to anxiety and seven relate to depression) with 4

197   response options, ranging from 0 to 3, with higher scores indicating worse symptoms. A

198 high sensitivity (82%), specificity (77%) and clinical utility index (.74) were reported

199 for the HADS (Mitchell et al., 2010). This study used a HADS version adapted to the

200 Mexican population with a good Cronbach's alpha (α =.86) resulting in a depression

201 cut-off point of 7 and an anxiety cut-off point of 8 (López- Alvarenga et al., 2002).

202 **Self-reported clinical outcomes**

203   **Activities, thoughts and mood diary**. Patients and caregivers were asked to

204 complete one diary in which they recorded the frequency of leisure activities, their

205 thoughts related to depression, anxiety, and cancer, and the patient's mood. According

206 to clinical experience and previous research (Greer et al., 2010), leisure activities were

207 defined as a patient's effort to engage in self-perceived pleasant activities consistent

208 with their declining health condition (frequency of leisure or home support activities

209 were fulfilled; see Table 3) Similarly, they were asked to write and describe negative

210 thoughts that could be associated with depression and anxiety. Finally, patients recorded

211 their moods on a daily basis and the most significant events, both positive and negative,

212 occurring in their everyday lives. Similar records have been used in patients with

213 advanced cancer (Lévesque et al., 2004).

214   Finally, relatives and patients were asked five open-ended questions once the

215 treatment was completed: From your perspective 1) What effects did the therapy have

216 on the depression/anxiety of the patient? 2) What were the most useful components you

217 observed in the therapy? 3) What were the most complicated components you observed

218 in the therapy? 4) Did the therapy cause any harm to the patient? And 5) What do you

219 think about the fact that this therapy was provided at your home? Similar interviews

220 have been used in patients with advanced cancer (Lévesque et al., 2004).

221 **Intervention**

222   Regarding the treatment, a cultural adaptation of CBT was conducted according

223   to the Mexican context. Further descriptive information is provided in Table 2. Study

224   staff convened meetings to standardize the intervention components and safeguard the

225   integrity of the treatment. Previous terminal cancer studies were reviewed to identify the

226   main components used in CBT for patients with depression and anxiety in general, and

227   for those with advanced cancer in particular (Greer, Graham, & Safren, 2009; Greer et

228   al., 2010). Based on this review, an intervention manual was developed detailing the

229   techniques used for each component of the therapy. Further descriptive information is

230   provided in Table 3. The modules were: 1) psycho-education on CBT principles

231   (Norcross, 2011; Padesky & Mooney, 1990); 2) relaxation training (Greer et al., 2010;

232   Stetter & Kupper, 2002); 3) identification and modification of negative thoughts related

233   to anxiety and depression (Greer et al., 2010; 2012); and 4) planning leisure activities as

234   well as strategies for physical symptoms (Greer et al., 2010). Following the review

235   conducted and considering that terminal cancer patients' physical condition worsens

236   with time, it was decided that the intervention would be provided in a range of four to

237   six sessions within a period of three weeks. Thus, the physical deterioration or death of

238   the patient could be anticipated. On average, the intervention was delivered in 4.6

239   sessions (range 4-6 sessions) over the course of 19 days (range of 11-26 days: 2.8

240   weeks). In eight out of nine patients, their relatives (wives, sisters, daughters, and

241   nieces) also attended the therapy; hence, primary caregivers were always present for

242   most sessions. Therapy was provided twice a week.

243   Treatment was delivered by the first author of this paper (he was a clinical

244   psychology graduate student at the time this study was conducted). Four other licensed

245   psychologists individually joined the therapy sessions with the sole purpose of acting as

246   independent assessors for the baseline-assessment and post-assessment, rating anxiety

247 and depression symptoms using the HADS, as well as completing a checklist on the

248 session's integrity. Three assessors took part in all sessions with two patients, and one

249 assessor took part in all sessions with three patients.

250   Six participants completed the CBT modules in the order outlined in the

251 treatment manual; however, three patients were very anxious at the beginning of the

252 therapy, which led to the clinical decision to start the intervention with the relaxation

253 training. Finally, according to the treatment integrity checklist, the nine patients

254 received all components included in the treatment manual.

255   [TABLE 2]

256   [TABLE 3]

257   Patients completed at home and with assessors' help the post-assessment scales

258 one week after completing the intervention. They also had weekly follow-up

259 assessments for approximately one month during which they continued to add entries to

260 their diaries and completed the HADS. In four cases, patients failed to complete the

261 one-month follow-up because they died.

262 **Data Analysis**

263   **Visual and statistical analyses.** Visual analysis was conducted according to the

264 suggestions of Kratochwill et al. (2010): six features were used to examine within- and

265 between- phase data patterns: 1) level, as represented by an average, 2) trend, 3)

266 variability, 4) immediacy of the effect: comparing the last three baseline phase

267 measurements to the first three intervention phase measurements, 5) overlap and 6)

268 consistency of data patterns across similar phases. The visual analysis was aided by the

269 website described in Manolov (2018). Regarding the statistical analysis, no gold

270 standard exists, because the different alternatives focus on different data features, and

271   all of them have advantages and flaws (Tate et al., 2013). We decided to use both

272   nonoverlap indices (Non-overlap of All Pairs index, NAP; Parker & Vannest, 2009 and

273   Tau-U; Parker, Vannest, Davis, & Sauber, 2011) and the between-cases standardized

274   mean difference (BC-SMD; Hedges, Pustejovsky, & Shadish, 2013).

275   BC-SMD was used to obtain an overall quantification of the difference between

276   baseline and intervention phase scores of anxiety and depression, both in raw and in

277   standardized terms. BC-SMD was obtained using the *scdhlm* package for R

278   (Pustejovsky, 2016a) and the website (Pustejovsky, 2016b). We performed two

279   different statistical analysis because: (a) the approaches focus on different aspects of the

280   data; (b) the nonoverlap indices offer a quantification for each participant separately,

281   whereas the BC-SMD offers an overall quantification; and (c) the results of several

282   effect size measures can be compared in order to assess the consistency of the results

283   (Kratochwill et al., 2010). The results of the visual and statistical analyses can be

284   replicated by using the raw data (available in Excel format at https://osf.io/q7uhe/) and

285   by executing the analyses via the websites mentioned above.

286   The BC-SMD represents the data in each phase using the phase means, that is,

287   as flat trend lines. In contrast, NAP and Tau-U do not model or reduce to data to a mean

288   or a trend line. NAP and Tau-U rather quantify the proportion of data points in the

289   intervention condition that are improve relative to baseline phase measurements

290   (Ledford, Lane, & Severini, 2018). NAP is closely related to the Mann-Whitney U test

291   (Parker & Vannest, 2009) and it can also be interpreted as a probability of superiority

292   (Grissom, 1994): the probability that a randomly selected intervention data point would

293   represent an improvement over a randomly selected baseline data point. Thus, NAP and

294   Tau-U represent ordinal measures (i.e., how many data points are improved after the

295   intervention), in comparison to the BC-SMD that measures the distance between the

296   measurements from different conditions (i.e., how large is the improvement). Finally,

297   the difference between NAP and Tau-U is that the latter allows accounting for

298   improving baseline trend. NAP and Tau-U were computed using a specific website

299   (Vannest, Parker, Gonen, & Adiguzel, 2016).

300   **Reliable Change Index/Clinically Significant Change**. The Reliable Change

301   Index/Clinically Significant Change (RCI/CSC) method was used to determine if

302   participants underwent considerable enough changes during their treatment, so that such

303   changes could be regarded clinically significant (Morley, & Dowzer, 2014). RCI/CSC

304   analysis was conducted by considering the nine patients separately for both anxiety and

305   depression scores. The first score from baseline was deemed the pre-treatment score,

306   and the last reported score was deemed the post-treatment score. Reliability for this

307   measure was obtained from mean values reported in a literature review of HADS

308   validity data (Bjelland, Dahl, Haug, & Neckelmann, 2002). Means and standard

309   deviation of clinical norms were obtained from a sample of palliative care patients being

310   treated at home (Austin, Wiley, McEvoy, & Archer, 2011) and comparison norms were

311   obtained from the general population normative data (Hinz et al., 2014). According to

312   Jacobson (1991), statistical criteria for defining Clinically Significant Change (CSC)

313   was that the level of functioning after therapy should fall outside the range of the

314   clinical population, in the direction of the reference group.

315   **Further assessment of self-reported clinical outcomes**

316   The non-parametric Wilcoxon signed-rank test was used to determine

317   differences in distributions of pooled data of behavioral activation during pre- and post-

318   treatment. A significance level of $p \leq .05$ was used to label differences as statistically

319   significant. Finally, the main disease-related negative thoughts are mentioned, as well as

320   the major clinical effects on the patient's functioning which were significant for patients

321 in our intervention. This assessment aligns well with the call to consider more carefully

322 the social validity (Snodgrass, Chung, Meadan, & Halle, 2018).

323 **Results**

324 **Depression**

325   Figure 1 shows the data for depression symptoms as outcome for the nine

326 subjects in the three cohorts.

327 The visual data analysis shows that nine patients reported elevated depression

328 symptoms at baseline. The baseline data were relatively stable for all patients, except

329 for the improving trend for patient 2 from cohort 3 and the deteriorating trend for

330 patient 3 from cohort 3. For patient 2 from cohort 1, and patient 1 from cohort 2 we

331 also decided to control for improving baseline trend using Tau-U instead of NAP,

332 although the trend was less clear. During phase B, all nine patients showed a small

333 overall decrease in level in their depression scores; this decrease was immediate for

334 most patients. For two of the participants (patient 1 from cohort 2 and patient 1 from

335 cohort 3) the scores were systematically in the normative range, whereas patient 3 from

336 cohort 3 also achieved this result at the end of the intervention. There is certain

337 (although far less than perfect) consistency of the decrease in depression across

338 participants.

339   [FIGURE 1]

340   Due to few clear trends observed in the data, we considered that the application

341 of the BC-SMD, which assumes lack of trend, was reasonable. The overall average

342 difference between baseline and intervention was -3.16 HADS score points,

343 representing a standardized mean difference of -0.76 (with a confidence interval

344 ranging from -1.33 to -0.21). Given that BC-SMD was created to be equivalent to

345   Cohen's *d* (Hedges et al., 2013), such a difference is very close to a large effect (0.80),

346   as per Cohen's (1992) benchmarks.

347   The values of the nonoverlap indices for each individual are presented in Table

348   4. There is a decrease for all participants, except for one. The NAP values indicate a

349   moderate effect (between 0.66 and 0.92, as per Parker and Vannest, 2009), whereas the

350   two (out of three) Tau-U negative values would represent a large change (between 0.60

351   and 0.80, according to Vannest & Ninci, 2015).

352   [TABLE 4]

353   An overall assessment of the scores in depression reveals that all intervention

354   phase averages are below the baseline averages and that for two individuals these

355   intervention averages are in the normative range.

356

357   **Anxiety**

358   Figure 1 shows the data for anxiety symptoms as outcome for the nine subjects

359   in the three cohorts.

360   The visual data analysis shows that only six subjects experienced elevated anxiety at

361   baseline. Patient 3 from cohort 1 shows a clear improving baseline trend. For patient 1

362   from cohort 2 and patients 2 and 3 from cohort 3 there could also be an improving

363   trend, but it is not that visually clear. In order to be conservative, we still controlled for

364   such trends by using Tau-U instead of NAP for these four participants. For most

365   participants there was an immediate change in level. In contrast, an improving trend and

366   a somewhat delayed change was observed during the intervention phase for two

367   participants: for patient 3 from cohort 2 and, to a lesser extent, for patient 1 from cohort

368   3. Among the participants whose anxiety scores were not in the normative range already

369   during the baseline phase, one participant (patient 1 from cohort 3) achieved normative

370   scores for most of the intervention phase measurements. Additionally, further four

371   participants (patient 2 from cohort 1, patient 3 from cohort 2, and patients 2 and 3 from

372   cohort 3) achieved normative anxiety scores for some intervention phase measurements.

373   The consistency of the decrease in anxiety across participants is rather low.

374   Due to few clear trends observed in the data, we again considered that the

375   application of the BC-SMD, which assumes lack of trend, was reasonable. The overall

376   average difference between baseline and intervention was −2.82 HADS score points,

377   representing a standardized mean difference of −0.54 (with a confidence interval

378   ranging from −0.94 to −0.17). Given that BC-SMD was created to be equivalent to

379   Cohen's *d* (Hedges et al., 2013), such a difference is very close to a moderate effect

380   (0.50), as per Cohen's (1992) benchmarks.

381   The values of the nonoverlap indices for each individual are presented in Table

382   5. There was a decrease for all participants, except for one. The NAP values indicate a

383   moderate effect (between 0.66 and 0.92, as per Parker and Vannest, 2009) for four of

384   the five participants. Regarding the three (out of four) negative (i.e., improving) Tau-U

385   values: one represents a small change (between 0 and 0.20), one represents a moderate

386   change (between 0.20 and 0.60), and one represents a large change (between 0.60 and

387   0.80, according to Vannest & Ninci, 2015).

388   Overall, for the anxiety scores, the intervention phase averages are below the

389   baseline averages for seven of the nine individuals. For five individuals the intervention

390   averages are in the normative range, but for four of them they were already normative in

391   the baseline.

392   **Adverse Events**

393   Given the extremely ill state of health of the patients, three patients died during

394   phase B (patients 2 and 3 from cohort 1; patient 2 from cohort 2), and one patient

395   developed delirium (patient one/cohort one). Patient 2 from cohort 3 experienced a

396   number of problematic stressors during therapy (his mother died, he got a car stolen and

397   his brother disappeared).

398   **Reliable Change Index/Clinically Significant Change**

399   It was found that 2 out of 9 patients (22.22%) had both a reliable and a clinically

400   significant change for depressive symptoms. Both patients had levels of depressive

401   symptomatology before the intervention well above the cut point posed by the

402   instrument (scores of 12 and 10) and reached levels just at the cut-off point (>7) and

403   well below it (1). Seven patients made no change but did not deteriorate with respect to

404   their symptoms of depression. Similarly, 3 out of 9 patients (33.33%) had both a reliable

405   and a clinically significant change in their anxiety symptoms. These patients had from

406   moderate to very high levels of anxious symptoms prior to the intervention (scores of

407   14, 14 and 17) and all of them decreased their levels below the cut-off point for anxiety

408   (>8).

409   **Self-reported clinical outcomes**

410   **Leisure Activities and Negative Thoughts**

411   For behavioral activation, the Wilcoxon signed-rank test was applied to compare

412   the value during pre- (12.5) and post-assessment (15.5). The result showed a statistically

413   significant increase (Z= 2.668, *p*= .008). Thus, CBT encouraged patients to increase

414   their leisure behaviors or to carry out other activities. It is important to mention that

415   many problems were faced in getting patients or their caregivers to complete their

416   behavior records, because they would do so intermittently or in a non-descriptive

417   manner. The psychology staff tried to complete behavioral records retrospectively with

418   patients whenever possible (retrospective records, 21%). Because records were not

419   available for every session, the average of weekly behaviors and thoughts of patients

420   were calculated (behavioral records missing, 34.5%) negative thoughts (missing thought

421   records, 36.2%; retrospective records, 16.5%). Similarly, the leisure activities record did

422   not follow a behavior coding protocol as recommended in recent studies by Busch,

423   Uebelacker, Kalibatseva & Miller (2010). We will return to this point in the limitations

424   section. In most cases, negative thoughts were not irrational but real and distressing;

425   therefore, therapists encouraged patients to change their thoughts for more adaptive and

426   comforting ones. Identified thoughts were classified according to frequency of

427   occurrence as follows: a) disease progression and physical symptoms, b) functionality

428   and daily activities, c) concerns related to loved ones, and d) social and financial

429   problems. These categories were created using the most frequent thoughts recorded in

430   patients' mood diaries and thoughts reported verbally during therapy.

431   All nine patients considered that CBT had positive effects which helped them to

432   control or reduce their mood, and none of them felt that the therapy caused them any

433   harm. Most patients (n=8/9) mentioned that autogenic relaxation and guided imagery

434   produced immediate tranquilizing effects. Additionally, these components helped

435   patients to find relief from negative physical symptoms such as pain or nausea, and they

436   deemed them easy to perform. For patients with limited capacity to go out, guided

437   imagery allowed them "to go" to places they liked (e.g., their hometowns, a beach, a

438   place in the forest) and to experience a pleasant feeling at that particular moment. The

439   intervention component that focused on changing negative thoughts was the most

440   challenging for patients. Those with a higher level of education found it easier to

441   understand the relationship between thoughts, feelings, behaviors, and physical

442   symptoms. Yet, for the remaining patients (6 out of 9), thought change required the

443   greatest assistance from the study therapist as well as help from their primary caregivers

444   so they could be reminded that these thoughts were creating negative feelings. All nine

445   patients seemed pleased to receive home-based therapy, and no patient considered it

446   invasive to their family privacy. For 8 out of 9 patients, therapy was delivered to both

447   the patient and the primary caregiver or family member. Therefore, it is probable that

448   caregivers also developed strategies to cope with the disease of their loved one. For

449   example, they practiced relaxation techniques and worked to modify negative thoughts

450   related to the disease and to the way they were living with their loved one's disease.

451   **Discussion**

452   **Interpreting and Integrating the Current Findings**

453   In this research, data showed that the intervention had moderate positive effects

454   in both depression and anxiety scores. The standardized mean differences (SMD)

455   obtained were pretty similar to those reported in a recent meta-analysis of

456   psychotherapy for depression (current research: −0.76; meta-analysis: −0.67) and

457   anxiety (current research: −0.54; meta-analysis: −0.65 as secondary outcome) among

458   advanced and incurable cancer patients (Okuyama et al., 2017). These similarities are

459   remarkable given the differences in research designs and participant characteristics in

460   each study. The present research was focused on terminally ill cancer patients very

461   close to their death while most of the international research was focused on advanced

462   cancer patients with a better middle-term prognosis, functionality and medical system

463   context than those in Mexico (Edelman et al., 1999; Greer et al., 2012; Lévesque et al.,

464   2004; Moorey et al., 2009; Savard et al., 2006).

465   This tailored CBT approach increased leisure behaviors in patients. Increased

466   self-reported behavioral activities are an important indicator of decreased depression

467   (Dobson & Dobson, 2009). It has also been reported that regardless of the deterioration

468   of the cancer patient, activities can be adapted so patients can carry them out in their

469   everyday lives, and this becomes an aid for a better emotional state (Greer et al., 2010;

470   Moorey & Greer, 2012). Similarly, changes in negative thoughts were observed.

471   Alternative thoughts that helped patients to feel calmer despite disease progression were

472   developed. Similar data have been reported in previous empirical studies where

473   modifying negative ideas became central to the emotional wellbeing of the advanced

474   cancer patient (Lévesque et al., 2004; Savard et al., 2006). Also, the classification of

475   negative thoughts described in the results of this paper could be helpful to further

476   understand and screen types of negative thoughts and their triggers in terminal cancer

477   patients in Mexico, and likely present in other developing countries. Additionally, it

478   might be useful to consider the portion describing that many patients with low schooling

479   levels had difficulties understanding some components of the therapy; particularly,

480   those related to cognitive restructuring. On this point, the international literature has

481   reported that a low schooling level is a distinctive condition of the Latin American

482   population. The recommendation is to identify and adapt the therapy components to the

483   cultural and educational situation of this population. Some suggestions are the use of

484   proverbs, consideration of participants' sociocultural environment when working on

485   behavioral activation, and incorporation of cultural values (Ramos & Alegría, 2014).

486   The cultural CBT adaptation was considered a helpful therapy for patients and

487   caregivers. These results were corroborated through the reports of caregivers who

488   perceived CBT to be positive and useful. It seems possible that this intervention led to

489   important outcomes for patients with a very high disease burden. Caregivers could

490   participate in the therapy together with the patient, which empowered caregivers to help

491   patients to remember and apply the content delivered during each therapy session. The

492   family structure and care given to patients could become an important factor to consider

493   for future research in terminal cancer patients (Ferrell et al., 2017), as well as protective

494   or supportive factors that make patients value having good social support networks. In

495   addition, the cultural adaptations of this therapy were helpful in ensuring that patients

496   did not stop therapy due to problems related to physical symptoms, transportation, or

497   lack of financial resources. Finally, using SCED in this population seems a viable

498   option to produce initial evidence on the effects of psychological intervention in

499   terminal cancer patients. It also seems to be an option to prevent terminal cancer

500   patients from being subjected to a long wait in control groups or while new intervention

501   groups are formed (waiting times can be of up to ten months; Edelman et al., 1999). The

502   SCED can prevent an increase in their physical deterioration or death before they

503   receive any therapeutic support.

504   **Limitations and Future Research**

505   Regarding the limitations of the data obtained in this research, it should be noted

506   that this study faced many clinical and methodological challenges during its

507   implementation. It is worrisome that only 9 (8%) out of 117 potential patients assessed

508   at the Palliative Care Department were healthy enough (i.e., could talk, pay attention,

509   and follow instructions) to receive psychological help. Anecdotally, most patients

510   passed away shortly after their first medical palliative assessment. This is a significant

511   problem for the healthcare system in Mexico, which fails to provide adequate and

512   timely cancer screening. Moreover, delayed medical referrals to palliative care and

513   failure to seek medical help have been associated with the high rate of deterioration of

514   cancer patients in Latin America and Mexico (Goss et al., 2013; Torres-Vigil, Aday, De

515   Lima & Cleeland, 2007). Additionally, some patients experienced distressing symptoms

516   during therapy, such as pain, vomiting, fatigue. Due to these symptoms, at times

517   therapists had to interrupt the session for some minutes to help the patient to feel better.

518   Understandably, the clinical application of therapy in this population is very

519   challenging.

520   To the extent possible, the Risk of Bias in N-of-1 Trials (RoBiNT) criteria were

521   followed to promote the internal and external validity of this study (Tate et al., 2013);

522   however, caution must be taken when generalizing the data in this research, particularly

523   in what pertains the following: when using a SCED it is advisable to have at least three

524   to five data points per phase in order to analyze single-subject data (Kratochwill et al.,

525   2010). This study was unable to collect at least five data points per phase because

526   patients' physical symptoms or deaths made it impossible to continue to collect such

527   records. Even though having a short baseline worked well for clinical and ethical

528   purposes, this decision might have prevented the criteria from achieving a more

529   complete and exhaustive analysis of the data collected. Also, given the nature of this

530   research, it was not possible to keep participants, investigators, and assessors unaware

531   of the intervention goals; therefore, blinding was not achieved.

532   Many problems were faced in getting patients or their caregivers to complete

533   their behavior records. Missing records is a common issue among Mexican patients, and

534   the international literature has reported the same problem in the field (Lévesque et al.,

535   2004). The behaviors that could be recorded were only included in the report filled out

536   by the patient and their relative. Although terminal cancer literature has proved this to

537   be a common and useful approach to avoid assigning more complex tasks to the patient

538   and their relative, current literature in general contexts has suggested that these methods

539   are not sophisticated enough. Therefore, there is an ongoing need for more reliable

540   measuring methods that lay out how to codify and analyze these behaviors (Busch et al.,

541   2010). Another consideration is that patients could have reported what they believed

542   researchers wanted to hear. Social desirability bias is a serious problem in research

543   involving self-report measurements, which can be true in behavioral and thoughts

544   records. Nevertheless, self-reporting tools seem to provide the most feasible

545   measurements for depression and anxiety in advanced cancer patients. To help avoid

546   this potential bias, independent researchers completed the assessments with the patients

547   and their relatives, explaining the importance of being honest and descriptive in their

548   reports. However, we did not measure whether this action had an effect on the accuracy

549   of the information provided by the patients and their relatives. A final consideration is

550   that we did not use a diagnostic interview to determine diagnoses of depressive or

551   anxiety disorders per a formal classification system. Yet, the literature has amply

552   reported the complexity of assessing the varied range of these disorders in the advanced

553   cancer population. The latter relates to the impossibility of identifying whether the

554   physical symptoms reported were due to anxiety or depression, the development of

555   cancer, or as a side effect of the treatment (Okuyama et al., 2017). Given the design

556   selected for this study and the limitations described above, the resulting data should be

557   taken as an initial approach to the effects of intervention. Further studies that may

558   confirm these findings are recommended.

559   **Implications of the Findings**

560   It seems that a tailored CBT intervention might be a successful clinical

561   approach for terminal cancer patients with depression and anxiety symptoms in the

562   Mexican context. Nevertheless, this therapy (or any psychological therapy) is not an

563   option for patients without sufficient performance status to participate in therapy. Sadly,

564   as described before, most of the Mexican terminal cancer patients are in this situation. It

565   is our hope that these findings help to encourage the Mexican Healthcare System to

566   overcome this barrier in order to provide better supportive care for this population.

567   Future institutional steps should develop campaigns aimed at identifying cancer at

568   earlier stages (Goss et al., 2013), as well as raising awareness on the benefits of

569   integrating palliative care early in the course of care for patients with metastatic cancer.

570   Research has indeed shown that in doing so, patients' quality of life, emotional distress,

571   and wellbeing will benefit (Ferrell et al., 2017; Temel et al., 2010). Finally, we can

572   conclude that brief, tailored home-based CBT might be a clinically valid option as an

573   aid to address anxiety and depression symptoms in Mexican patients with terminal

574   cancer who are close to their death.

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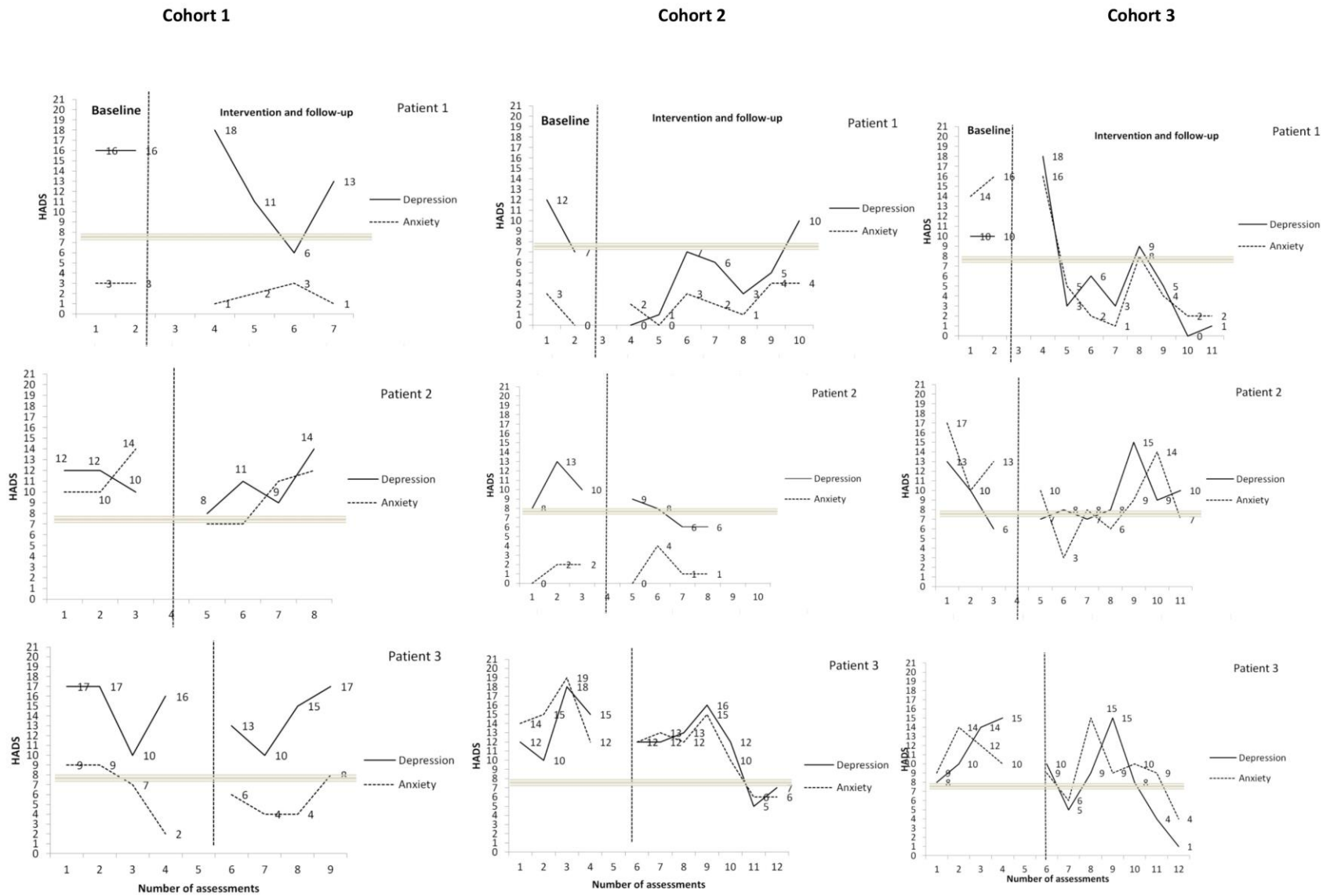823   *Psychiatrica Scandinavica*, *67*(6), 361–370.

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Figure 1. HADS score of depression and anxiety symptoms for the nine participants from the three cohorts

Table 1. Demographic characteristics of each patient

Participant	Age	Sex	Edu.	Functionality	Cancer diagnosis	Mood problem	Medication*	Life span+
Patient 1, Cohort 1	81	F	IES	Mostly in bed (PPS=40)	Kidney cancer/lung and liver metastases	Depression	None	88 days
Patient 2, Cohort 1	49	F	IES	Slow and limited ambulation (PPS=60)	Cervical cancer/stomach metastasis	Depression & anxiety	None	64 days
Patient 3, Cohort 1	69	M	IES	Slow and limited ambulation (PPS=60)	Colon cancer/liver metastases	Depression & anxiety	None	79 days
Patient 1, Cohort 2	44	M	HS	No evidence of disease (PPS=90)	Pancreatic cancer/liver metastases	Depression & anxiety	Fluoxetine**	302 days
Patient 2, Cohort 2	65	F	IES	Normal activity with effort (PPS=80)	Pancreatic cancer/thyroid metastasis	Depression	None	64 days
Patient 3, Cohort 2	83	F	TC	Mainly on couch and bed (PPS=50)	Cervical cancer/bone metastases	Depression	None	493 days
Patient 1, Cohort 3	63	M	ES	Inability to perform activities at home (PPS=70)	Liver cancer/stomach metastasis	Depression & anxiety	None	160 days
Patient 2, Cohort 3	76	M	ES	Normal activity with effort (PPS=80)	Liver cancer/stomach metastasis	Depression & anxiety	Fluoxetine**	89 days
Patient 3, Cohort 3	40	F	TC	Mainly on chair and bed (PPS=50)	Ovarian cancer/uterus metastasis	Depression & anxiety	None	Information not available

Note: F=Female; M= Male; Edu.=Education; IES=Incomplete elementary school; ES=Elementary school; HS=High School;

TC=Technical career; PPS=Palliative Performance Scale; *= Psychotropic Medication; **=20 milligrams per day; +=From the

first assessment at the Palliative Care Department until the day they died.

Table 2. Cultural adaptation of CBT in the context of advanced cancer in Mexico

Mexican Cultural elements	Resulting adaptation
Short life expectancy	Brief therapy (4-6 sessions) in three weeks
Distressing physical symptoms	Psychological techniques for anxiety and physical symptoms
	Home-based therapy reducing the burden of travel on patients and families who may be unable to visit the hospital due to illness and symptoms
Poverty	Home-based therapy reducing the burden of travel on patients and families who may be unable to visit the hospital due to lack of financial resources. Treatment protocol was adapted to socioeconomic and psychosocial contextual issues
Limited formal education	Simple examples of CBT components were used. Examples of patient's daily life events were used
Extended family structure	Flexibility for integrating extended family into CBT therapy A lot of sessions in the study were provided on weekends before the meal time when all the relatives were together
Language and idiosyncrasies	Treatment in the study was provided using the cultural meaning of Mexican-Spanish words. Cultural likes were taken to create better relationship and understanding of concepts

Note: CBT= Cognitive Behavioral Therapy

Table 3. Components of cognitive behavioral therapy manual for anxiety and depression

Module	Objectives	Techniques
I. Psycho-education on CBT principles	Create a good therapy relationship between patient and therapist	Alliance Empathy Goal Consensus and collaboration
	Help patients identify the relationships among thoughts, behaviors and feelings	Review CBT model within context of patients daily life.
II. Relaxation training	Teaching patients to use a variety of relaxation techniques in order to control anxiety and physical symptoms	CD or MP3 with directions about: Autogenic relaxation Guided imagery Pursed-lip breathing
III. Negative thoughts related to anxiety and depression	Identify and modify negative thoughts associated with anxiety and depression in terminal cancer	Review CBT model of anxiety and depression within context of terminal cancer Identify negative thoughts related to the disease Change negative thoughts with more adaptive and comforting thoughts
IV. Planning activities and strategies for managing physical symptoms	Identify and engage in leisure behaviors or activities that patients could perform according to their daily physical capacities Reinforce patients' efforts to focus their attention on pleasant events to help tolerate distressing physical symptoms	Some activities proposed by patients were: Watching classical Mexican movies; watching soccer matches of the FIFA World Cup; watching Mexican soap operas; reading books; reading the bible; listening to religious songs; visiting with family; walking around a nearby park; sunbathing; helping make a meal; cleaning small objects around the house; fixing things around the house; singing; telling stories of their life to their grandchildren; playing with their young children; weaving; or playing with bird seeds or beads

Table 4. NAP and Tau-U indices values for depression and anxiety

Participant	Index	Value	90% Confidence interval
	Depression		
Patient 1, Cohort 1	NAP	−0.75	−1 to 0.39
Patient 2, Cohort 1	Tau-U	−0.67	−1 to 0.11
Patient 3, Cohort 1	NAP	−0.66	−1 to 0.40
Patient 1, Cohort 2	Tau-U	−0.71	−1 to 0.09
Patient 2, Cohort 2	NAP	−0.88	−1 to 0.03
Patient 3, Cohort 2	NAP	−0.60	−0.85 to 0.44
Patient 1, Cohort 3	NAP	−0.88	−1 to 0.04
Patient 2, Cohort 3	Tau-U	0.05	−0.64 to 0.74
Patient 3, Cohort 3	NAP	−0.81	−1 to −0.02
	Anxiety		
Patient 1, Cohort 1	NAP	−0.88	−1 to 0.14
Patient 2, Cohort 1	NAP	−0.67	−1 to 0.44
Patient 3, Cohort 1	Tau-U	−0.06	−0.78 to 0.65
Patient 1, Cohort 2	Tau-U	0.36	−0.45 to 1
Patient 2, Cohort 2	NAP	−0.54	−0.86 to 0.69
Patient 3, Cohort 2	NAP	−0.84	−1 to -0.06
Patient 1, Cohort 3	NAP	−0.91	−1 to -0.03
Patient 2, Cohort 3	Tau-U	−0.71	−1 to -0.03
Patient 3, Cohort 3	Tau-U	−0.53	−1 to 0.07

Note: Negative results indicate decrease (i.e., improvement). Note that the standard errors used to construct the confidence intervals of NAP and Tau-U assume independent data.