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Jongen, Peter; Ruimschotel, Rob P.; Museler-Kreijns, Y. M.; Dragstra, T. M. C.; Duyverman, L.; Valkenburg-Vissers, J.; Cornelissen, J.; Lagrand, R.; Donders, Rogier; Hartog, A.

Published in:
Journal of pain research

DOI:
10.2147/JPR.S137609

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Download date: 23-12-2018
Improved health-related quality of life, participation, and autonomy in patients with treatment-resistant chronic pain after an intensive social cognitive intervention with the participation of support partners

Abstract: Despite the availability of various specific treatments, most patients with chronic pain (CP) consider their pain problem as undertreated. Recently, multiple sclerosis (MS) patients who were given an intensive 3-day social cognitive treatment with the participation of support partners experienced lasting improvements in health-related quality of life (HRQoL) and self-efficacy. In this study, a similar intervention was given to treatment-resistant CP patients with stressors, relational problems with support partner, and distress, anxiety or depression. Before and 1, 3, and 6 months after the intervention, patients completed the Euro-Qol 5 Dimensions 5 Levels (EQ-5D-5L) and Impact on Participation and Autonomy (IPA) questionnaires (primary outcomes), and the Survey Of Pain Attitudes (SOPA), the Four-Dimensional Symptom Questionnaire (4DSQ) (distress, depression, anxiety, and somatization), and Visual Analog Scale for pain outcomes), and the Survey Of Pain Attitudes (SOPA), the Four-Dimensional Symptom Questionnaire (4DSQ) (distress, depression, anxiety, and somatization), and Visual Analog Scale for pain intensity, whereas the support partners completed the Caregiver Strain Index (CSI) questionnaire. Differences between baseline and post-treatment were tested via paired t-tests (significance level 0.05). Of the 39 patients who were included, 34 (87.2%) completed the 3-day treatment. At 1, 3, and 6 months, improvements were seen in EQ-5D-5L-Index (+40.6%; +22.4%; +31.7%), Health Today (+61.8%; +36.3%; +46.8%), Control attitude (+45.8%; not significant [NS]; +55.0%) and decreases in IPA-Problems (−14.8%; −20.4%), Harm attitude (−18.9%; −15.0%; −17.7%), Distress (−17.7%; −31.8%; −37.1%), and Depression (−37.4%; −31.4%; −35.7%) scores. The CSI score had decreased by −29.0%, −21.4%, and −25.9%, respectively. In conclusion, after an intensive 3-day social cognitive intervention, treatment-resistant CP patients experienced substantial and lasting improvements in HRQoL and in problematic limitations to participation and autonomy, in association with improvements in pain attitudes, depression, and distress. To assess whether this innovative approach may be an effective treatment for this subgroup of CP patients, future randomized controlled studies are needed.

Keywords: goal setting, depression, anxiety, distress, caregiver, caregiver strain, pain attitudes

Introduction

Despite increased understanding of the factors contributing to the development of chronic pain (CP), the population burden of CP is rising.1 In the Netherlands, about 18% of the general population experience a moderate to severe pain condition, and studies performed in different settings have demonstrated that CP affects between 10% and 30% of the adult population in Europe.2-4 CP is associated with a number
of negative outcomes including reduced health-related quality of life (HRQoL), impairment of function, limited daily activities, isolation, depression, and helplessness.\textsuperscript{1,4,5} As a result, CP constitutes a considerable burden to patients, their families, and the society.\textsuperscript{5}

Of Dutch CP patients with a pain score of 5 or higher on a Visual Analog Scale (VAS) (0–10), 57\% is being treated.\textsuperscript{2} As to treatment modalities, 41\% of the patients use analgesics, mainly nonsteroidal anti-inflammatory drugs. Among the non-pharmaceutical therapies, physiotherapy, acupuncture, and massage are the most frequent ones, whereas cognitive behavioral treatment is hardly applied.\textsuperscript{5} However, despite various specific treatment options and recommendations, >56\% of CP patients in the Netherlands declare that their pain problem is undertreated and 78\% of patients with a VAS score of ≥5 state that they experience their treatment as insufficient.\textsuperscript{5}

Analogous to the situation in multiple sclerosis (MS), a chronic and disabling disorder of the central nervous system, pain-induced disability may lead to helplessness and negatively affect patients’ independence and autonomy.\textsuperscript{5,7} The negative experience of losing independence may cause CP patients to underestimate their capacities, as a result of which they have a risk to further lose existing functions. As a reaction to the loss of autonomy, patients tend to externalize or objectify their pain and want medications or medical cure to solve the pain problem. Moreover, CP patients often expect their significant others to be solicitous in response to their pain. Indirectly, informal caregivers, like partners, family, and friends, are confronted as well with the impact of an increase in disabilities and a decrease in independence. In fact, the patients’ continuous and increasing appeal to support partners may result in an ever-increasing pressure on the latter.

For patients with MS and their support partners, the Can Do treatment was developed, which is an intensive multidisciplinary 3-day social cognitive intervention.\textsuperscript{6,7} The Can Do treatment is based on the social cognitive theory, according to which psychosocial functioning is determined by reciprocal interactions between personal factors, behavior, and the environment.\textsuperscript{8,9} The goal is to enable patients to regain access to their capabilities and thus to improve their autonomy and HRQoL. In persons with relapsing remitting (RR) MS, it was observed that half a year after this treatment, mental and physical HRQoL had increased by 22.3\% and 17.6\%, respectively.\textsuperscript{6} In a subsequent study, it was found that 12 months after treatment, RRMS patients had an increased physical HRQoL (+15.0\%) and decreased depression (−29.8\%) and anxiety (−25.9\%).\textsuperscript{10}

Given the chronic and disabling nature of both CP and MS, and the resemblances in the processes that may lead to loss of autonomy and HRQoL, it was considered that an intervention similar to that in MS might be effective in treatment-resistant CP patients. Therefore, based on the Can Do treatment for RRMS patients, the Challenge intervention was developed and assessed for its potential effects.

**Methods**

**The Challenge**

The concept, components, and multidisciplinary approach of the Challenge intervention are based on those of the Can Do treatment in MS, which has been described in detail.\textsuperscript{6,7,10} Methodologically, it is of note that CP patients and their professional caregivers are often convinced that the pain problem can be controlled and cured by medication, injections, or other invasive procedures, whereas MS patients are familiar with the notion that their disorder is as yet incurable. Hence, the dependence and loss of autonomy in CP patients are expectedly greater than that in MS patients.

**Concept**

The purpose of the intervention is to unveil and stimulate existing capacities, with “stressor” as the central concept.\textsuperscript{6,7,10} The Challenge is primarily sociologically oriented\textsuperscript{6,7,10} and aims to identify those stressors that limit patients in their physical, psychological, or social role activities.\textsuperscript{6,7,10} To reduce stressors, the intervention is based on five principles: identification and reduction of existing stressors; client-centeredness; inclusion of support partner (partner or a significant informal caregiver); group sessions; and the central notions of self-reliance, autonomy, and acceptance.\textsuperscript{6,7,10} The intervention aims to reduce relevant stressors, to push personal boundaries, and to establish new ones by making maximal use of the existing potential.\textsuperscript{6,7,10} In order to put the patient’s capacities in a realistic context, central mottos are “Can,” “Will,” “Choose,” “Open up to others,” and “Do.”\textsuperscript{6,7,10} Thus, patients get an increased awareness of their potential which may result in better self-management and interactions with professional caregivers.\textsuperscript{6,7,10}

**Components**

The components of the Challenge are similar to those of the Can Do treatment in MS, which have been described in detail.\textsuperscript{6,7,10} In brief, large and small group sessions, consultations, a theater evening, and an optional collective activity at the start of the day.\textsuperscript{6,7,10} In the plenary sessions, patients and partners make optimal use of their capacities, learn how
to support and stimulate others, and how to give feedback to the team of professionals;6,7,10 in sessions with half of the participants, major stressors are identified and each person names at most two realizable aims.6,7,10 Then, during group consultations, the participants check if the goals can be realized.6,7,10 Depending on his/her aim(s), each participant registers for various small sessions, which form the actual intervention.6,7,10 In “Body” sessions, coached by a physiotherapist, physical capacities are explored;6,7,10 the “Feeling” sessions, coached by a psychiatric nurse and a psychiatrist, deal with the exploration of the emotional potential.6,7,10 and in the “Life” sessions, coached by a registered pain consultant and an anesthesiologist specialized in pain, the potentials regarding daily living with CP are explored.6,7,10 Moreover, participants can also choose for the relaxation sessions “Dance” and “Physical.”6,7,10

Multidisciplinary team
The multidisciplinary team includes a psychiatrist, psychiatric nurse, anesthesiologist specialized in pain, registered pain consultant, physiotherapist, and dance therapist.

Study design and organization
Various clinical outcomes were prospectively measured in CP patients and their support partners before and after treatment. The determination of the size of the study group was based on two considerations: first, in the observational study, in 44 MS patients, statistically significant and clinically relevant changes were found in the RR subgroup of 20 patients,6 and, second, the presumed similarities in psychological mechanisms underlying the HRQoL impairments in RRMS and CP patients.

The Challenge is based on the Can Do treatment that was developed by the National Multiple Sclerosis Foundation (Rotterdam, the Netherlands), PsyToBe, and members of the Can Do team.6,7,10 The study was initiated and financed by DC Klinieken Rotterdam (Rotterdam, the Netherlands). The Challenge interventions were organized by DC Klinieken Rotterdam, and the study was designed and performed by MS4 Research Institute (Nijmegen, the Netherlands). Patients were recruited by DC Klinieken Rotterdam from the outpatient population of the clinic.

The eligibility criteria for patients were 1) CP diagnosis, 2) positive pre-screening (see below), 3) able and willing to participate in the study and the study-related assessments, 4) written informed consent, and 5) having a support partner who is willing and able to participate in the study and the study-related procedures.6,7,10 The eligibility criteria for support partners were 1) willing and able to participate in the study and 2) written informed consent.6,7,10

The pre-screening was performed by an anesthesiologist specialized in pain (AH) and a registered pain consultant (YMM-K) (DC Klinieken Rotterdam) in an outpatient setting during regular visits. Patients were assessed for no or insufficient response to standard treatments (treatment-resistance), evidence suggestive of the existence of stressors, evidence suggestive of relational problems between patient and support partner, and abnormally high score(s) on the distress, anxiety, or depression sub-scale(s) of the Four-Dimensional Symptom Questionnaire (4DSQ).

Assessment schedule and data acquisition
Data were obtained through the online versions of psychometrically validated questionnaires and VAS at baseline (1 week before treatment) and 1, 3, and 6 months after treatment. This assessment schedule was similar to that used in the Can Do treatment studies in MS patients. After having given their consent, the patients were sent a personal code to gain access to the study website.10 The assessments were performed online via the LimeSurvey software.10 The questionnaires had fixed items, and responses were captured automatically.10 The processes of data acquisition and storage were in accordance with the European Union regulations regarding online medical data.10 Before submission, the questionnaires were verified automatically for completeness. In case patients had not filled in the questionnaires within 1 week after schedule, they were given a phone call by the help desk as a reminder.10

Outcomes and outcome measures
The primary study outcomes were changes in 1) HRQoL and 2) participation and autonomy at 6 months after treatment. Secondary outcomes were changes in 1) pain intensity, 2) pain attitudes, and 3) distress, anxiety, depression, and somatization 6 months after treatment. The tertiary outcome was change in care-related strain perceived by the support partner 6 months after treatment.

Primary outcome measures
HRQoL was assessed by using the Euro-Qol 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire, a standardized measure of health status.11,12 The EQ-5D-5L provides a descriptive profile, a single index value for health status, and a VAS score for Health Today.12 The instrument is designed for self-completion by respondents and is cognitively undemanding.12 The EQ-5D-5L comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/
Each dimension has five levels: no problem, slight problems, moderate problems, severe problems, and extreme problems or not able to. The respondent is asked to indicate his/her health state by ticking in the box against the most appropriate statement in each of the five dimensions, which results in a 1-digit number expressing the level selected for that dimension. A resulting 5-digit number describes the respondent’s health state, and the health states may be converted into a single index value. The VAS records the respondent’s answer to the question “We would like to know how good or bad your health is today” by means of a vertical VAS (0–100) with endpoints labeled “The best health you can imagine” and “The worst health you can imagine.” The EQ-5D-5L-Index value and the VAS score were calculated.

Secondary outcome measures

Pain intensity was assessed through a VAS (0–10) by using three questions: 1) “What is the degree of your pain at this moment?” 2) “What was the degree of your pain at a moment that the pain was minimal?” 3) “What was the degree of your pain at a moment that the pain was maximal?”

Patients’ attitudes and beliefs about pain were assessed by means of the Survey Of Pain Attitudes (SOPA) questionnaire. The SOPA consists of seven scales that are divided into two areas – adaptive beliefs and maladaptive beliefs. According to its authors,


Tertiary outcome measure

The burden to support partners was assessed by the Caregiver Strain Index (CSI). The CSI is a 13-item instrument that identifies strain of informal care providers. Each item is scored yes (=1) or no (=0), and addition of the item scores yields the CSI score (0–13). A higher CSI score indicates a higher caregiver strain. A score of ≥7 indicates a high level of stress, and therefore a need for more in-depth assessment to facilitate appropriate intervention (positive screen).

Ethical aspects

The protocol was approved by the “Medisch-Ethische Toetsing Onderzoek Patiënten” (METOPP), an ethical review
board residing in Tilburg, the Netherlands; CCMO (Central Committee on Research Involving Human Subjects) number: NL.49040.028.14 (http://www.ccmo.nl/en). The study was carried out in compliance with the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects version 2013; 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) (www.wma.net) and the Dutch Medical Research Involving Human Subjects Act of 1999 (www.wetten.overheid.nl/BWBR0009408). Patients received no financial incentive or reward to participate. As the intervention, like the Can Do treatment in MS, forms an exceptional physical and mental strain, it may lead to a transitory increase in pain or to changes in mood and emotions. The experience of the team members safeguarded that adverse effects were immediately addressed.

Data analysis
For all outcomes, the absolute values at baseline and at 1, 3, and 6 months after the intervention were calculated (mean, standard deviation [SD], minimum, and maximum). The changes at 1, 3, and 6 months, expressed as percentages of baseline, were calculated as well (mean, standard error of the mean [SEM], and median). As the purpose of the study was to assess whether and when clinically relevant changes occurred after treatment, we compared each post-treatment outcome with its baseline value using multiple paired Student’s t-tests and expressed the change as percentage of the baseline value. To prevent multiple testing from interfering with a sound interpretation of the data, conclusions were based on the 6-month primary outcomes.

Post hoc we explored the relationship between the pain, HRQoL, and distress/anxiety scores, and between the EQ-5D-5L and VAS scores at baseline and at 6 months by calculating Pearson’s correlation coefficient (r).

For all tests, a P-value <0.05 was considered significant. The statistical analyses were performed at the Department for Health Evidence of the Radboud University Medical Centre (Nijmegen, the Netherlands).

Results
Patients
Of the ~700 patients who were seen at the outpatient clinic between January and July 2014, 87 were positive for treatment resistance and existence of stressors and of relational problems between patient and support partner. Of these, 75 patients had abnormally high score(s) on distress, anxiety, or depression 4DSQ subscale(s), and 39 of these were willing to participate. Thus, 39 patients with support partners were included, completed the baseline assessments, and started the Challenge.

The patients had 49 CP diagnoses. The most frequent diagnoses were lumbar radicular pain (n=15), failed back surgery syndrome (n=8), cervical radicular pain (n=7), fibromyalgia (n=4), postoperative cervical pain (n=2), and posttraumatic stress disorder (n=2), whereas abdominal pain, arthrosis, chondropathy, eye pain, lumbar disk collapse, lumbar pain, pain left buttock of unknown origin, and chronic widespread pain were each diagnosed in one patient. Ten patients had two diagnoses.

The patients used in total 37 different pain-related medications. The median number of drugs used per patient was 3 (minimum 0, maximum 5). The medications that were most frequently used were tramadol (n=10), amitriptylin (n=9), paracetamol (n=9), pregabalin (n=7), etoricoxib (n=6), and fentanyl (n=6). Other medications were buprenorfin, diolfinac, and ibuprofen (each four times); celecoxib, citalopram, gabapentin, paroxetine, and sumatriptan (each three times); clonazepam, codeine, oxazepam, oxycodone, rifaziparin, and venlafaxine (each twice); and clomipramine, diazepam, dipiperon, dolutexine, fluoxetine, imipramine, lidocaine, lithium, lorazepam, mirtazapine, morphone, prilocaine, sertraline, temazepam, zolmitriptan, zolpidem, and zopiclone (each once).

The marital status were: married (n=18), living together with partner (n=8), living alone (n=6), living alone with child(ren) (n=4), and living apart together (n=3). The employment status were: receiving sickness benefit (n=11), employed (n=8), unemployed (n=5), receiving disability benefit (n=5), retired (n=4), and voluntary work (n=2). In seven patients, the employment status was unknown, and three patients were partly employed, partly receiving sickness or disability benefit.

Four interventions were given in 2014 (March, May, September, and November), each during 3 consecutive days, in the hotel The Arendshoeve (Bergambacht, the Netherlands). Nine to ten patients and support partners participated in each intervention. Five (12.8%) patients and their support partners prematurely discontinued, whereas 34 (87.2%) completed the 3 days. The reasons for early discontinuation were: “Treatment is irritating and humiliating” (male, 31 years, pain duration 1 year, failed back surgery syndrome, group 1); “This is nonsense, information beforehand was insufficient” (male, 38 years, pain duration 6 years, lumbar radicular pain, group 1); “I absolutely don’t want to work in groups” (male, 44 years, pain duration 30 years,
abdominal pain, group 3); “I am too restless for the treatment, I am unable to manage it” (female, 70 years, pain duration 2 years, lumbar radicular pain, group 3); “I am very angry about all this” (female, 51 years, pain duration 20 years, cervical radicular pain, group 4). In consequence of the reasons given by the two dropout patients in the first group, for the groups 2–4 a less confronting approach was adopted, without however changing the very concept of the Challenge.

Considering that in the dropout patients the intended changes would have occurred partially or not at all, these patients were not included in the effectiveness analyses. Of the 34 patients who completed the intervention, 26 (76.5%) were female and eight (23.5%) male. Their mean age was 48.9 years (SD 12.6) (minimum 20.0, maximum 74.0) and were female and eight (23.5%) male. Their mean age was 48.9 years (SD 12.6) (minimum 20.0, maximum 74.0) and the mean pain duration was 8.4 years (SD 9.6) (minimum 0.5, maximum 33.2). All 34 analyzable patients performed the baseline assessment, 33 of these (97.1%) performed the 1-month assessment, 28 (82.4%) the 3-month assessment, and 29 (85.3%) the 6-month assessment.

HRQoL, participation, and autonomy
The mean, SD, minimum, and maximum values for the EQ-5D-5L-Index, the VAS Health Today, and the IPA-Limitations and IPA-Problems scores at baseline and 1, 3, and 6 months after intervention are presented in Table 1. At 6 months, the EQ-5D-5L-Index, the VAS Health Today score, and the IPA-Problems score were evidently increased as compared to baseline (all \(P\leq0.007\)) (Table 1; Figure 1A–C).

Pain intensity, pain attitudes, distress, depression, anxiety, and somatization
The mean, SD, minimum, and maximum values for the VAS Actual, Minimum and Maximum pain intensity, the attitudes SOPA Control, Emotion, Disability, Harm, Medication, Solicitude, and Medical, and the 4DSQ symptoms Distress, Depression, Anxiety, and Somatization at baseline and 1, 3, and 6 months after intervention are presented in Table 2. Statistically significant and substantial changes were observed in Actual pain intensity (decreased), the attitudes Control (increased) and Harm (decreased), and the symptoms Distress and Depression (both decreased) (all \(P\leq0.0095\)) (Figure 1D–G). In addition, statistically significant decreases were also seen in the attitudes Disability (\(P=0.0461\)), Solicitude (\(P=0.0457\)), and Medical Cure (\(P=0.0300\)), and the symptoms Anxiety (\(P=0.0204\)) and Somatization (\(P=0.0173\)) (Table 2, Figure 1H).

Caregiver strain
The mean CSI score at 6 months was lower than before intervention (\(P=0.0222\)) (Table 3; Figure 1I). Whereas before intervention, 41% of the support partners had a CSI \(\geq7\), at 6 months post-intervention, this was 32%.

Percentage changes from baseline
To assess whether statistically significant changes could be interpreted as clinically relevant, that is, improvement, the post-intervention values were expressed as percentages of the baseline values. It was found that at 6 months, the EQ-5D-5L-Index and VAS Health Today had increased by 31.7% (mean) and 46.8% (mean), respectively, whereas the IPA-Problems score had decreased by −20.4% (mean) (Table 4A). As to the secondary outcomes, the attitudes Control and Harm had changed by +55.1% (mean) and −17.7% (mean), respectively, and the symptoms Distress, Depression, and Somatization had decreased by −37.1% (mean), −35.7% (mean), and −16.8% (mean), respectively (Table 4B). Moreover, the Actual pain intensity had decreased by −14.6% (mean). Finally, the CSI score had decreased by −25.9% (mean) at 6 months (Table 3).

### Table 1 Mean (SD) (minimum–maximum) EQ-5D-5L-Index, VAS Health Today, IPA-Limitations, and IPA-Problems values at baseline and at 1, 3, and 6 months after intervention

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Baseline (n=34)</th>
<th>Month 1 (n=33)</th>
<th>Month 3 (n=28)</th>
<th>Months 6 (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D-5L-Index</td>
<td>0.43 (0.21) (−0.03–0.79)</td>
<td>0.57 (0.22) (0.02–0.84) ((P\leq0.0001))</td>
<td>0.54 (0.24) (0.11–0.87) ((P=0.0091))</td>
<td>0.56 (0.22) (0.17–0.87) ((P=0.0012))</td>
</tr>
<tr>
<td>VAS Health Today</td>
<td>37.6 (16.2) (7–65)</td>
<td>55.9 (19.9) (12–80) ((P=0.0001))</td>
<td>48.1 (24.1) (10–85) ((P=0.0162))</td>
<td>46.4 (25.3) (8–83) ((P=0.0021))</td>
</tr>
<tr>
<td>IPA-Limitations</td>
<td>2.1 (0.6) (1–3)</td>
<td>1.9 (0.7) (1–3) ((P=0.0335))</td>
<td>2.1 (0.7) (0–3) ((P=0.9971))</td>
<td>1.9 (0.8) (1–3) ((P=0.1138))</td>
</tr>
<tr>
<td>IPA-Problems</td>
<td>1.3 (0.4) (0–2)</td>
<td>1.1 (0.5) (0–2) ((P=0.0552))</td>
<td>1.1 (0.5) (0–2) ((P=0.0276))</td>
<td>1.1 (0.6) (0–2) ((P=0.0070))</td>
</tr>
</tbody>
</table>

Note: \(P\)-values for comparisons between baseline and post-intervention.

**Abbreviations:** EQ-5D-5L, Euro-QoL 5 dimensions 5 levels; IPA, Impact on Participation and Autonomy; SD, standard deviation; VAS, visual analog scale.
Post hoc analyses

It was found that at baseline (n=34) none of the pain scores correlated with the EQ-5D-5L-Index, the VAS Health Today, the 4DSQ Anxiety score, or the 4DSQ Distress scores (all P>0.06). However, the 4DSQ Distress score correlated with the EQ-5D-5L-Index (Pearson’s r =-0.58; P=0.000) and the Health Today score (r=0.343, P=0.047), and the 4DSQ Anxiety score also correlated with the EQ-5D-5L-Index (r=-0.474; P=0.005) score.

At 6 months (n=29), the Actual, Minimal, and Maximal pain scores correlated with the Health Today score (r=-0.57, P=0.001; r=-0.37, P=0.048; r=-0.51, P=0.005), and the Actual and Maximal pain scores also correlated with the EQ-5D-5L-Index (r=-0.56, P=0.002; r=-0.55, P=0.002). Similar to baseline, the 4DSQ Distress score correlated with the EQ-5D-5L-Index (r=-0.77; P=0.000) and the Health Today score (r=-0.501, P=0.006), and the 4DSQ Anxiety score correlated with the EQ-5D-5L-Index (r=-0.563; P=0.001).

Figure 1 Scatter plots visualizing individual responses for those outcomes that showed statistically significant changes at six months. The X-axis represents the score at baseline, and the Y-axis the score at 6 months after the intervention.

Abbreviations: CSI, Caregiver Strain Index; EQ-5D-5L, Euro-Qol 5 Dimensions 5 Levels; IPA, Impact on Participation and Autonomy; SOPA, Survey Of Pain Attitudes; VAS, visual analog scale.
Table 2 Mean (SD) (minimum–maximum) values for VAS Actual, Minimum and Maximum pain, SOPA attitudes Control, Emotion, Disability, Harm, Medication, Solicitude, and Medical, and 4DSQ symptoms Distress, Depression, Anxiety, and Somatization at baseline and at 1, 3, and 6 months after intervention

<table>
<thead>
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<th>Month 3 (n=28)</th>
<th>Months 6 (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual pain (0–10)</td>
<td>6.7 (1.9) (0–10)</td>
<td>6.1 (2.1) (2–10)</td>
<td>6.1 (1.7) (2–9)</td>
<td>5.7 (2.3) (2–9)</td>
</tr>
<tr>
<td>(P=0.2808)</td>
<td>(P=0.4385)</td>
<td>(P=0.0095)</td>
<td></td>
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</tr>
<tr>
<td>Minimal pain (0–10)</td>
<td>3.7 (1.8) (0–7)</td>
<td>3.6 (2.0) (0–7)</td>
<td>4.0 (2.0) (1–8)</td>
<td>3.7 (2.0) (0–8)</td>
</tr>
<tr>
<td>(P=0.7704)</td>
<td>(P=0.2668)</td>
<td>(P=0.6676)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal pain (0–10)</td>
<td>8.3 (2.2) (0–10)</td>
<td>7.8 (1.7) (4–10)</td>
<td>7.8 (1.8) (0–9)</td>
<td>8.0 (1.8) (2–10)</td>
</tr>
<tr>
<td>(P=0.3093)</td>
<td>(P=0.6590)</td>
<td>(P=0.2676)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>47.2 (6.3) (34–59)</td>
<td>50.0 (9.6) (28–68)</td>
<td>49.1 (10.6) (26–68)</td>
<td>52.2 (10.2) (24–78)</td>
</tr>
<tr>
<td>(P=0.0476)</td>
<td>(P=0.1867)</td>
<td>(P=0.0035)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotion</td>
<td>52.1 (11.5) (30–80)</td>
<td>55.1 (12.5) (38–80)</td>
<td>52.7 (12.1) (30–80)</td>
<td>54.4 (11.1) (30–80)</td>
</tr>
<tr>
<td>(P=0.0602)</td>
<td>(P=0.8262)</td>
<td>(P=0.4765)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td>54.2 (9.0) (40–74)</td>
<td>50.7 (10.0) (28–72)</td>
<td>53.4 (9.7) (40–72)</td>
<td>51.1 (12.6) (25–74)</td>
</tr>
<tr>
<td>(P=0.0233)</td>
<td>(P=0.6226)</td>
<td>(P=0.0461)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harm</td>
<td>55.2 (8.1) (42–74)</td>
<td>51.0 (9.8) (34–76)</td>
<td>54.0 (10.5) (36–80)</td>
<td>51.8 (10.3) (28–72)</td>
</tr>
<tr>
<td>(P=0.9313)</td>
<td>(P=0.0256)</td>
<td>(P=0.0027)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>47.5 (6.7) (31–59)</td>
<td>47.7 (6.6) (37–62)</td>
<td>47.4 (6.6) (35–59)</td>
<td>46.8 (5.7) (33–59)</td>
</tr>
<tr>
<td>(P=0.0016)</td>
<td>(P=0.8103)</td>
<td>(P=0.0029)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solicitude</td>
<td>48.2 (10.2) (32–80)</td>
<td>48.8 (10.0) (32–63)</td>
<td>45.2 (10.8) (32–65)</td>
<td>46.1 (12.1) (32–72)</td>
</tr>
<tr>
<td>(P=0.0025)</td>
<td>(P=0.0538)</td>
<td>(P=0.0457)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical cure</td>
<td>54.8 (7.7) (34–75)</td>
<td>52.1 (6.3) (34–63)</td>
<td>51.6 (8.0) (36–75)</td>
<td>50.1 (9.8) (27–66)</td>
</tr>
<tr>
<td>(P=0.0095)</td>
<td>(P=0.0070)</td>
<td>(P=0.0300)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distress</td>
<td>20.4 (8.1) (7–32)</td>
<td>15.8 (8.9) (1–32)</td>
<td>14.5 (10.4) (0–32)</td>
<td>14.4 (10.4) (0–32)</td>
</tr>
<tr>
<td>(P=0.0018)</td>
<td>(P&lt;0.0001)</td>
<td>(P=0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>4.7 (4.5) (0–12)</td>
<td>3.0 (3.7) (0–12)</td>
<td>3.5 (4.6) (0–12)</td>
<td>3.6 (4.4) (0–12)</td>
</tr>
<tr>
<td>(P=0.0023)</td>
<td>(P=0.0262)</td>
<td>(P=0.0072)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.7 (5.8) (0–20)</td>
<td>4.0 (4.9) (0–20)</td>
<td>3.6 (5.2) (0–21)</td>
<td>3.6 (5.3) (0–21)</td>
</tr>
<tr>
<td>(P=0.0271)</td>
<td>(P=0.1853)</td>
<td>(P=0.0204)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatization</td>
<td>17.2 (4.5) (9–26)</td>
<td>14.7 (5.1) (7–26)</td>
<td>14.5 (5.2) (4–26)</td>
<td>14.0 (6.9) (3–29)</td>
</tr>
<tr>
<td>(P=0.0098)</td>
<td>(P=0.0233)</td>
<td>(P=0.0173)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: P-values for comparisons with baseline. Abbreviations: SD, standard deviation; SOPA, Survey Of Pain Attitudes; VAS, visual analog scale; 4DSQ, Four-Dimensional Symptom Questionnaire.

Table 3 CSI (mean) (SD) (minimum–maximum) values at baseline and at 1, 3, and 6 months after intervention; CSI percentage changes (mean) (SEM) (median) post-intervention; and the number (Nr) (percentage) of support partners with a CSI ≥7 at various time points

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Baseline (n=29)</th>
<th>Month 1 (n=27)</th>
<th>Month 3 (n=26)</th>
<th>Month 6 (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSI (0–13)</td>
<td>5.6 (3.3) (0–11)</td>
<td>3.7 (2.7) (0–9)</td>
<td>4.1 (3.4) (0–11)</td>
<td>4.4 (3.7) (0–12)</td>
</tr>
<tr>
<td>(P=0.0008)</td>
<td>(P=0.0264)</td>
<td>(P=0.0222)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSI % Δ (SEM) (median)</td>
<td>−29.0% (9.7) (−37.5%)</td>
<td>−21.4% (10.2) (−25.0%)</td>
<td>−21.4% (10.2) (−25.0%)</td>
<td>−25.9% (8.7) (−26.1%)</td>
</tr>
<tr>
<td>(P=0.0065)</td>
<td>(P=0.0467)</td>
<td>(P=0.0069)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nr. (%) CSI ≥7</td>
<td>12 (41%)</td>
<td>4 (15%)</td>
<td>5 (19%)</td>
<td>8 (32%)</td>
</tr>
</tbody>
</table>

Note: P-values for comparisons with baseline. Abbreviations: CSI, Caregiver Strain Index; SD, standard deviation; SEM, standard error of mean.

The correlation between the EQ-5D-5L-Index and VAS Health Today score at 6 months (r=0.836, P=0.000) was higher than that at baseline (r=0.604, P=0.000).

Discussion

A half year after having received an intensive social cognitive intervention, in which their support partners participated, treatment-resistant CP patients with evidence of stressors, relational problems with support partner, and distress, anxiety or depression showed an increased HRQoL and less problems with limitations to participation and autonomy. The 6-month data also suggest beneficial changes in the attitudes Control and Harm, and the symptoms Distress and Depression.

As percentage changes of 15%–20% or higher may be considered clinically relevant,21 the degree of HRQoL increase (EQ-5D-5L-Index +32%, Health Today +47%) and of the decrease in problematic limitations to participation
and autonomy (IPA-Problems −20.4%) may be qualified as improvements. Similarly, the changes in the Control (+55%) and Harm (−18%) attitudes, and in the symptoms Distress (−35%) and Depression (−35%) may be qualified as clinically relevant as well. Alternatively, an indication about clinical relevance can also be obtained by expressing changes as SD of the baseline scores. Thus, compared to baseline, at 6 months the EQ-5D-5L-Index was +0.62 SD baseline, Health Today +0.54 SD baseline, IPA-Problems −0.50 SD baseline, Control attitude +0.70 SD baseline, Harm attitude −0.42 SD baseline, Distress −0.74 SD baseline, and Depression −0.24 SD baseline. So, except for Depression, two different approaches suggest that the statistically significant changes mentioned above are indeed clinically relevant. Moreover, the improvements seemed to occur as early as 1 month after the intervention and were more or less maintained up to 6 months later.

Assessment of HRQoL is increasingly considered essential in patients with chronic disorders. HRQoL is an overall measure of well-being from the patient’s perspective which provides a comprehensive measure of health status. It can be defined as the functional effect of an illness and its subsequent therapy upon a patient, as perceived by the patient. In general, in CP patients, HRQoL is inversely related to the degree of pain. The average mental well-being score for men and women in severely limiting CP is at a similar level to that of the lowest scoring 10% of people who are pain free. Against this background, the improvement in EQ-5D-5L-Index (mean +31.7%) and VAS Health Today (+46.8%) in our selection treatment-resistant patients suggests that an eventual effectiveness of the Challenge approach could indeed be relevant from the patient’s perspective.

Although the limitations in participation and autonomy had not changed, the degree at which patients experienced

Table 4  Mean percentage change (standard error) (median) from baseline for the primary and secondary outcome measures

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Month 1 (n=33)</th>
<th>Month 3 (n=28)</th>
<th>Months 6 (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(A) Primary outcome measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D-5L-Index</td>
<td>+40.6% (9.9) (+32.2%)</td>
<td>+22.4% (8.6) (+11.4%)</td>
<td>+31.7% (10.9) (+10.4%)</td>
</tr>
<tr>
<td>VAS Health Today</td>
<td>+61.8% (12.5) (+37.5%)</td>
<td>+36.3% (12.8) (+23.0%)</td>
<td>+46.8% (21.4) (+16.7%)</td>
</tr>
<tr>
<td>IPA-Limitations</td>
<td>NS</td>
<td>NS</td>
<td>+10.4% (7.5) (+4.9%)</td>
</tr>
<tr>
<td>IPA-Problems</td>
<td>−14.8% (5.4) (−12.7%)</td>
<td>NS</td>
<td>−20.4% (7.5) (−11.1%)</td>
</tr>
<tr>
<td><strong>(B) Secondary outcome measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual pain</td>
<td>NS</td>
<td>NS</td>
<td>−14.6 (6.2) (−0.0%)</td>
</tr>
<tr>
<td>Minimal pain</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal pain</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Control</td>
<td>+45.8% (18.7) (+23.5%)</td>
<td>NS</td>
<td>+55.1% (18.3) (+31.6%)</td>
</tr>
<tr>
<td>Emotion</td>
<td>+50.7% (20.9) (11.2) (P=0.0212)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Disability</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Harm</td>
<td>−18.9% (8.1) (−21.4%) (P=0.0267)</td>
<td>−15.0% (5.8) (−9.6%) (P=0.0158)</td>
<td>−17.7% (6.4) (−9.5%) (P=0.0095)</td>
</tr>
<tr>
<td>Medication</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Solicitude</td>
<td>−16.8% (7.5) (−9.1%) (P=0.0328)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Medical cure</td>
<td>NS</td>
<td>−13.2% (6.4) (16.5%) (P=0.0487)</td>
<td>NS</td>
</tr>
<tr>
<td>Distress</td>
<td>−17.7% (7.6) (−21.9%) (P=0.0252)</td>
<td>−31.8% (6.9) (−19.8%) (P=0.0001)</td>
<td>−37.1% (6.6) (−33.3%) (P=0.0001)</td>
</tr>
<tr>
<td>Depression</td>
<td>−37.4% (8.8) (−33.3%) (P=0.0003)</td>
<td>−31.4% (10.6) (−8.3%) (P=0.0076)</td>
<td>−35.7% (8.7) (−33.3%) (P=0.0004)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Somatization</td>
<td>−11.7% (4.6) (−16.7%) (P=0.0172)</td>
<td>−12.9% (6.2) (−15.1%) (P=0.0455)</td>
<td>−16.8% (6.7) (−13.0%) (P=0.0181)</td>
</tr>
</tbody>
</table>

Notes: P-values for comparisons with baseline. *Comparison based on n=26; NS (P>0.05). †Nonsignificant (P>0.05). ‡P=0.0556.

Abbreviations: EQ-5D-5L, Euro-Qol 5 Dimensions 5 Levels; IPA, Impact on Participation and Autonomy; NS, not significant; VAS, visual analog scale.
limitations as problematic had improved. This may relate to the co-occurring increase in the Control attitude, which indicate that patients believed stronger that they could control their pain. Similarly, a stronger belief to be able to control pain-induced limitations may be thought to result in experiencing these limitations as less problematic.

CP patients more often have problems with depression or anxiety than people with no pain, and the likelihood of reporting depression or anxiety increases markedly as pain grade increases. In the UK, 70% of men and 68% of women with high disability-severely limiting pain report being depressed or anxious, compared with 26% of men and 27% of women with low disability-low intensity pain, and 17% and 22% among those with no CP. A recent study in Spain showed that about 30% of CP patients felt sad/very sad or anxious/very anxious, and 47.2% considered their pain affected their families. Against this background, it is likely that the improvements that occurred in depression and distress have been instrumental in improving HRQoL.

Interestingly, 6 months after intervention, the CSI score had decreased by a mean of −25.9% (−0.36 SD baseline), indicating that the patients’ improvements were mirrored by a decrease in caregiver burden. It is of note that in the CSI, “strain” refers to those enduring problems that have the potential for arousing threat, a meaning that establishes “strain” and “stressor” as interchangeable concepts. Despite that care giving has been recognized as an activity with both perceived burdens and benefits, caregivers are prone to depression, grief, fatigue, changes in social relationships, and physical health problems. Moreover, perceived caregiver burden has been associated with patient reports of unmet needs. Therefore, screening tools are useful to identify care givers who would benefit from a more comprehensive assessment. As to the CSI, a total score of ≥7 is a positive screen and indicates a need for more in-depth assessment. Various domains have been identified that should be addressed in a comprehensive assessment of the care giving process: the patient’s cognitive status and problematic behaviors, and the caregiver’s perception of role overload or deprivation in key relationships, goals, or activities. Given that CP patients and their support partners both participated in the Challenge, and in view of the clinically relevant changes in patient-reported outcomes, it may be hypothesized that an improvement in patients’ problematic behaviors as well as in caregivers’ perception of role overload have contributed to the decrease in caregiver strain.

According to the social cognitive theory, patients can acquire knowledge directly by observing others within the context of social interactions and experiences. When patients observe others performing a behavior and the consequences of that behavior, they remember the sequence of events and use this information to guide subsequent behaviors. The Challenge is a group intervention with support partners, in which CP patients are challenged to take action and are stimulated to use their potentials and to perform new behavior. By observing each other’s behavior and experiencing the consequences, patients are able to perform this newly learned behavior in daily life, thus reducing the predominance of their pain and increasing their quality of life.

The Challenge intervention methodology for CP patients is based on the Can Do methodology designed around patients with MS. CP patients and MS patients have several similarities, that is, both suffer from chronic disorders causing anxiety, sleep disturbances, and depressive symptoms. Despite these similarities, it is important to note the differences between the Challenge intervention and the Can Do treatment. In the studies on the Can Do treatment, MS patients were included by a patient organization (National Multiple Sclerosis Foundation, the Netherlands), and patients were not screened for predictors that would supposedly enhance the chance of success of the Can Do approach. In contrast, CP patients for the Challenge intervention were included in a pain referral center by an anesthesiologist specialized in pain and a registered pain consultant, using a pre-screening for the existence of no or insufficient response to standard treatment, evidence suggestive of the existence of stressors, evidence suggestive of relational problems between patient and supporting partner, and abnormally high levels of distress, anxiety, or depression. By using this pre-screening procedure, only patients with chronic, complex, and treatment-resistant pain syndromes were eligible, being effectively 10%–15% of the patient population of the center. This difference in patient selection may in part explain why at 6 months in the CP group the mean increases of the two HRQoL measures (EQ-5D-5L-Index and Health Today) were +31.7% and +46.8%, respectively, whereas in the RRMS group the physical and mental HRQoL scores had on average increased by +17.6% and +22.3%, respectively. Moreover, in the RRMS patients, the IPA-Problems score showed a nonsignificant change of −3.9%, whereas the decrease in the CP patients was on average −20.4%.

Another difference is that RRMS patients are familiar with the notion that their disorder is as yet incurable. On the contrary, CP patients are often convinced that the anesthesiologist specialized in pain can control or cure the pain. Therefore, CP patients are likely to remain hopeful to be
relieved of the pain, thus becoming dependent on the treating physician with a greater loss of autonomy. Furthermore, in contrast to RRMS patients, high levels of stress work counterproductive for CP patients: their decreased autonomy and loss of control cause a higher sensitivity to stress compared to RRMS patients. The aim of the Challenge intervention is to reduce the relevant stressors, and this is accomplished by confrontation techniques, that is, to push personal boundaries and to establish new personal boundaries by making maximal use of the existing potential. In CP patients, the confrontation techniques may be experienced as an additional stressor. In consequence, the stress level may rise too high, leading to anxiety symptoms, a fight-flight-freeze reaction and in the end in regressive behavior and patient dropout. When we noticed this during the first session, we used less confronting techniques.

The additional explorative analyses suggest that the intervention may have resulted in a stronger relationship between pain and quality of life, without substantially affecting the existing relationship between distress and quality of life. Given that at 6 months patients had a higher Control attitude, a lower Harm attitude, were less depressed, and experienced their limitations on participation and autonomy as less problematic, it may be hypothesized that after the intervention these four factors impacted quality of life to a much lesser degree than at baseline, thus leading to a relatively stronger effect of pain on quality of life.

The questionnaires used in this study were psychometrically validated instruments. The EQ-5D-5L is a preference-based measure of HRQoL that enables comparisons between various patient populations and healthy controls. It is practical, reliable, valid, and responsive in patients with chronic diseases, especially family function, is considered, and in veterans, posttraumatic stress disorder symptoms were associated with punishing responses to pain from significant others. In young CP patients, family functioning was associated with functional ability, and parent distress may increase the risk of poor response to psychological treatment.

In CP patients, the social domain can have a greater impact on patients’ quality of life than any other aspect of pain, and recent research has focused on CP patients’ ability to participate in social and recreational activities. Against this background, the clinically relevant decrease in problematic limitations to participation and autonomy is in favor of the Challenge. In line with the social cognitive approach, group sessions were an integral part of the intervention, aimed to discover and exchange information about personal stressors and emotions. Interestingly, a qualitative study of cognitive behavioral group treatment in CP patients showed that an active role with self-revelation and exchanges of thoughts and feelings in the group may be instrumental in achieving therapeutic success. The exercise component in the Challenge is supported by an observational study in refractory CP patients, which found that a combination of behavioral therapy and exercise given to groups of individuals was followed by improvements in disability and pain intensity. Finally, a recent systematic review of CP in youth showed that depression, anxiety, and pain intensity were associated with higher levels of disability, and thus lends support to the supposed role of changes in depression, anxiety, and pain intensity in effectuating an improvement in HRQoL in our patients.
It has been suggested that psychological treatments, like social cognitive interventions, should be differentiated, for example, according to diagnosis, symptom severity or predictors.\(^1\)\(^,\)\(^4\)\(^5\)\(^4\)\(^6\)\(^7\) Actually, the Can Do treatment for RRMS patients and the Challenge intervention for CP patients differ in the degree at which confronting techniques are applied. A comparison of the Can Do and the Challenge study results suggests that in CP patients, prescreening for treatment resistance and starting points for the Challenge approach – that is, stressor(s), relational problems with support partner and high level of distress, anxiety, or depression – may have been crucial in bringing about a seemingly greater effect. Recent randomized controlled trials showed that in persons with chronic widespread pain, a short course of telephone-based cognitive behavioral therapy was effective and highly cost-effective long term\(^1\)\(^7\) and that in patients on sick leave due to chronic low back pain, cognitive behavioral therapy and physical group exercise were not effective compared to a brief, cognitive intervention.\(^6\) Hence, it is conceivable that (subgroups of) CP patients may benefit from a limited, outpatient version of the Challenge.

Our study has several limitations. First, as there was no control group, it cannot be concluded that there is a causality between the intervention and the improvements we noticed. Second, the patients were recruited in a single pain expertise and referral center in the Netherlands (DC Klinieken Rotterdam) and therefore generalizability of our findings may be questioned. Third, it is likely that especially patients experiencing a high level of pain and pain-related problems have volunteered for an intensive experimental intervention and that therefore a regression-to-the-mean effect has been operative. Fourth, uncontrolled studies cannot differentiate the intervention’s effect from a placebo effect; although after 6 months, a placebo effect is unlikely to fully explain the observed improvements. Fifth, after the first group, we modified the intervention slightly by adopting a less confronting approach; this, however, did not affect the very concept of the intervention. Sixth, the participants were not instructed to complete the questionnaires on the same time of day, and we did not ask for the time point of completion; given the variability in pain and other symptoms, this may have interfered with the validity of the study results.

Conclusion
Treatment-resistant CP patients with stressor(s), relational problems with support partner, and distress, anxiety or depression experienced improvements in HRQoL and in problematic limitations to participation and autonomy, a half year after having received an intensive social cognitive intervention with participation of support partners. Support partners experienced less caregiver strain. Our findings suggest that clinically relevant changes in the attitudes Control and Harm, and in Depression and Distress may have been operative in bringing about these improvements. To conclusively demonstrate the effectiveness and clinical relevance of the Challenge intervention in treatment-resistant CP patients, a randomized controlled trial is needed.

Acknowledgments
We greatly acknowledge the contribution of Marco Heerings (MH-Advies en organisatiebureau, Assen, the Netherlands) to the online acquisition of the data and of Wim Lemmens (Radboud University Medical Centre, Department for Health Evidence) to the statistical analysis.

Author contributions
PJJ performed the conception and design of the study, coordination, data acquisition, analysis, and interpretation; he also drafted the manuscript. RR conceived and developed the treatment, was involved in the organization of the study, was a member of the multidisciplinary team, took part in data analysis and interpretation, and co-drafted the manuscript. YMM-K, TMCD, and AH took part in the development of the intervention, study organization, and data acquisition; they were part of the multidisciplinary team and revised the manuscript critically for important intellectual content. LD, JV-V, JC, and RL were involved in the development of the treatment, were members of the multidisciplinary team, have been involved in the acquisition of the data, and have revised the manuscript critically for important intellectual content. RD has been involved in the analysis and interpretation of the data and has revised the manuscript critically for important intellectual content. All the authors read and approved the submitted manuscript.

Disclosure
YMM-K, TMCD, and AH are employees of DC Klinieken Rotterdam. PJJ received fees for consultancy activities or unrestricted research grants from Bayer, Merck, Mylan, and TEVA. The other authors report no conflicts of interest in this work.

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