Safety of “pain exposure” physical therapy in patients with complex regional pain syndrome type 1

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A B S T R A C T

“Pain exposure” physical therapy (PEPT) is a new treatment for patients with complex regional pain syndrome type 1 (CRPS-1) that consists of a progressive-loading exercise program and management of pain-avoidance behavior without the use of specific CRPS-1 medication or analgesics. The aim of this study was to investigate primarily whether PEPT could be applied safely in patients with CRPS-1. Twenty patients with CRPS-1 were consecutively enrolled in the study after giving informed consent. The diagnosis of CRPS-1 was defined using the Bruehl and Harden/IASP diagnostic criteria. CRPS-1 was diagnosed between 3 and 18 months after the inciting event (trauma). According to a multiple single-case design (baseline [A1], treatment [B], follow-up [A2]), multiple baseline and follow-up measurements were performed to evaluate changes in CRPS signs and symptoms and to assess functional parameters. When comparing the baseline with the follow-up phase, patients improved significantly with respect to pain on the visual analogue scale (57%), pain intensity (48%), muscle strength (52%), arm/shoulder/hand disability (36%), 10-meter walking speed (29%), pain disability index (60%), kinesiophobia (18%), and the domains of perceived health change in the SF-36 survey (269%). Three patients initially showed increased vegetative signs but improved in all other CRPS parameters and showed good functional recovery at follow-up. We conclude that PEPT is a safe and effective treatment for patients with CRPS-1.

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1. Introduction

Complex regional pain syndrome type 1 (CRPS-1), or reflex sympathetic dystrophy (RSD), is defined by the International Association for the Study of Pain as a pain syndrome that can develop after a physical injury (e.g., a fracture, sprain, or surgery) and that appears to be disproportional to the inciting event [23]. The disorder is characterized by pain (spontaneous pain, allodynia, or hyperalgesia), abnormal regulation of blood flow and sweating, edema, and trophic changes in skin, muscle, and bone [4,14]. The treatment of patients with CRPS-1 remains subject to discussion because of the difficulty of diagnosis [40,41], the unresolved pathophysiology and the clinical variability. Recently, a multidisciplinary Dutch task force published a comprehensive, evidence-based guideline for the treatment of CRPS-1 [27]. In this guideline, the World Health Organization (WHO) analgesic ladder is advised, with the exception of strong opioids, whereas for neuropathic pain anticonvulsants and tricyclic antidepressants may be considered. For inflammatory symptoms, free-radical scavengers are advised. To promote peripheral blood flow, vasodilatory medication or percutaneous sympathetic blockades may be indicated. To decrease impairments in function, activity limitations, and participation restrictions, standardized physiotherapy and occupational therapy are advised [26,27].

Although treatment according to this guideline may be effective in some cases, a large group of CRPS patients do not sufficiently respond to the treatment and may progress to chronic CRPS-1 with associated disabilities and restrictions in daily life [11,24,43]. Despite a variety of interventional drug treatments and guidelines, there is a need for a more comprehensive and possibly more effective treatment of patients with CRPS-1. Pain exposure physical therapy (PEPT) has been shown to be a promising comprehensive treatment for patients with longstanding (mean duration...
2. Methods

2.1. Subjects

Patients were recruited and treated at the multidisciplinary CRPS outpatient clinic of the Radboud University Nijmegen Medical Centre in The Netherlands. This is a Level 1 trauma center with a tertiary referral center for patients with CRPS. Our multidisciplinary CRPS team consists of a surgeon, anesthesiologist, rehabilitation physio- cian, and physical therapist. Each year, an average of 115 new patients with a probable CRPS are referred for diagnosis and treatment. All of these patients were screened for eligibility. The diagnosis of CRPS-1 was strictly made according to the Bruehl and Harden/IASP diagnostic criteria with a limitation of 18 months between the inciting event and current presentation [2,23] (Table 1). Patients with a minimum age of 18 years were consecutively enrolled in the study after oral and written informed consent. All patients received extensive information about the background of the study and PEPT treatment. Patients with neurological or psychiatric disorders and/or CRPS-1 in more than 1 extremity were excluded.

2.2. Study design

The study was designed as a multiple single-case design consisting of 3 phases: baseline, treatment, and follow-up (A1–B–A2 design) [21]. Baseline measurements in phase A1 (duration 4 weeks) were performed weekly and were performed at least twice before initiating PEPT treatment. Four measurements took place during treatment phase B (duration between 4 weeks and 3 months). Each measurement was performed several hours before the treatment session. In the follow-up phase A2 (duration 12 months), measurements were performed at 6 weeks, 3 months, 6 months, and 12 months after the last treatment session. A blinded and independent assessor (A.B.) who was not involved in the PEPT treatment or patient care performed all measurements and data processing. The assessor knew that the patient participated in the study but was not aware of the study phase for each patient. The study was approved by the local ethical committee (CMO No. 2008/274), and there were no conflicts of interest with other parties.

2.3. Intervention

During the study, all CRPS-related medications were gradually stopped. A progressive-loading exercise program was carried out by a team of 2 physical therapists. Cognitive-behavioral aspects were taken into account to motivate the patients to be more active and to use the painful limb in daily activities. Patients were expected to define clear treatment goals in the domains of activities and participation. The treatment aimed to decrease pain behavior and to increase self-confidence in the patients’ own physical possibilities. Living without adaptations or living independently from caregivers, returning to work and employment, and restarting domestic life, self-care, mobility, hobbies, and sports were the main treatment goals. Pain relief itself was not a primary treatment goal, and patients were informed that an increase in pain during or after the exercises and activities might occur. Patients were reassured that an increase in pain was not a sign of injury or tissue damage. In this respect, all conscious and unconscious signs of catastrophizing and kinesiophobic behavior were specified and talked through with the patient and his or her partner. If, despite explanation, doubt remained about the treatment content or when patients were not motivated to act upon instructions of the therapists, the treatment was stopped. The treatment consisted of progressive-loading exercises and desensitization beyond the patients’ pain limits. To decrease the enhanced skin sensitivity for touch and pressure, desensitization was carried out using self-massage and forced use of the affected arm or leg in daily activities. Homework exercises are a crucial aspect of PEPT. The treatment sessions mainly consisted of rehearsing and testing the homework exercises. The progressive-loading exercises were tailored and focused on specific body functions using standard techniques in regular physical therapy, including passive and active exercises to mobilize joints and muscle stretching. During progressive loading, the physical therapists acted mainly as instructors, rewarding functional progression and providing schedules for exercises and activities at home. Complaining about pain was discouraged, and it was no longer a subject of debate or a reason to reduce the treatment intensity. The length of the PEPT treatment period and the number of PEPT sessions varied among patients depended on the recovery rate and on patients’ satisfaction with achieved treatment goals. The treatment consisted of a maximum of 6 sessions (5 treatment sessions and 1 control session) of 1 h each, spread over the maximum treatment phase of 3 months.

2.4. Outcome measures

Safety of PEPT was the primary aim of the study, and therefore, the primary outcome measures were chosen to detect changes at
the level of severity of CRPS signs and symptoms during the phase of PEPT treatment (B), including measures of body functions (pain, swelling/edema, temperature, skin color, and active range of motion), activities, participation and personal factors, according to the domains of the International Classification of Functioning, Disability and Health [13]. The selection of these outcome parameters also provided data on the efficacy of this approach as a secondary aim of this study. All these measurements were subsequently taken 3 to 4 times per study phase and averaged for each phase of the design.

2.4.1. Body function

Edema. An independent assessor judged the presence of swelling between the affected and the healthy side at several levels: fingers/toes; hand/wrist and forearm/upper leg.

Skin temperature. Skin temperature was measured using an infrared thermometer (GENIUS, Covidien, Mansfield, MA). Standardized positions were used and averaged. A difference of $2^\circ$ centigrade was defined as clinically relevant because the measurement error of the skin temperature assessment was at least $1^\circ$ Celsius. To prepare for these measurements, patients adapted to room temperature before the measurements for at least 15 min with the extremities uncovered.

Skin color was judged by an independent assessor for the presence of differences in skin color between the affected and the healthy side.

Maximal pain intensity was measured using a visual analogue scale (VAS; 0–100) [5,33].

Pain experience was evaluated using the McGill Pain Questionnaire. The McGill Pain Questionnaire consists primarily of 3 major classes of word descriptors—sensory, affective, and evaluative—that are used by patients to specify their subjective pain experience. It also contains an intensity scale and other items to determine the properties of pain experience. The 3 major measures are the following: (1) the pain rating index (PRI-t), based on 2 types of numerical values that can be assigned to each word descriptor; (2) the number of words chosen (NWC-t); and (3) the present pain intensity based on an intensity scale of 1 to 5 measuring the total pain [22,42].

Joint mobility (in degrees) was evaluated using a goniometer by measuring differences between the affected and unaffected side with respect to the active range of motion of the wrist, hand, and finger joints in patients with CRPS-1 at the upper extremity. In patients with CRPS-1 at the lower extremity, the active range of motion of the ankle, foot, and toes was measured. A sum score was calculated by counting the individual separate joint mobilities. The individual difference between the affected and unaffected side with respect to the active range of motion in the A1 phase was calculated and set to 100%.

Muscle strength (Newton) of the upper extremity (grip-strength) with a Jamar dynamometer [20] and of the lower extremity (plantar flexion strength) with a Microfet2 hand-held dynamometer was measured. To control for the intersubject variance in muscle power, the difference between the affected and unaffected side was calculated. To control for the broad range of inter-subject side differences, the individual A1 baseline side difference was calculated and set to 100%.

2.4.2. Activities and participation

Function of the arm, shoulder, and hand was assessed by the Disability of Arm, Shoulder and Hand (DASH) measure [8,44] using only the first subscale. The DASH-DLV (Dutch Language Version) is a self-report questionnaire measuring, and the first subscale measures disability severity, with 23 questions all ranging from 1 (no difficulty) to 5 (impossible to do), with a total score range from 0 to 100. Item scores can be added up and used as total scores.

Walking capacity was measured with the 10-meter walking test (in seconds), which measures the time it takes to walk 10 meters [30,48] and with the timed up-and-go test (in seconds), which measures the time necessary to get up from a chair, walk 3 meters, go back to the chair and sit down again [29].

Disabilities associated with pain were measured with the Pain Disability Index (PDI) [15,37]. The PDI measures to what extent (from 0 to 10) activities of daily living including work are disabled because of pain. A high score (maximum 10) is completely disabled, whereas a score of 0 indicates no disability. The PDI consists of 7 items with a total score range from 0 to 70.

2.4.3. Personal factors

Kinesiophobia was measured with the Tampa Scale for Kinesiophobia (TSK) Dutch Language Version [36]. We used the 13-item questionnaire instead of the original 17-item scale. The 4 questions that were left out examine the inverse aspects of kinesiophobia. On this scale, patients with the highest possible degree of kinesiophobia have 52 points, and patients with no kinesiophobia have at least 13 points.

Quality of life was measured with the RAND 36-item Health Survey (version 1.0), a replica of the content of the MOS SF-36 [46]. It yields 8 concepts of quality of life: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. In this study only the subscale ‘general health’ (5 items; ranging from excellent to poor) and the ‘perceived change in health’ (1 item; ranging from ‘much better’ to ‘much worse’ now than 1 year ago) were used. Each item of the RAND 36-Item Health Survey version 1.0 is coded on a scale of 0 to 100 so that the lowest and highest possible scores are set at 0 and 100, respectively. After recoding items are averaged together per subscale to create the 8 subscale scores (0–100). A higher score of the subscales ‘general health’ and ‘perceived change in health’ indicates better perceived general health and change in health.

2.5. Statistical analysis

Data were analyzed at the individual level for each patient and at the group level using SPSS version 16.0 statistical software (SPSS Inc, Chicago, IL). For each patient the average was calculated for each outcome measure per treatment phase. Comparisons between the treatment phases (A1, B, and A2) were computed and statistically compared using Kruskal–Wallis followed by Mann–Whitney U tests for non-normally distributed variables and by paired Student’s t-tests for normally distributed variables. Averaging the baseline values per subject and putting the mean at 100% corrected interindividual differences in the baseline values for the active range of motion, muscle strength and walking capacity. Consequently, the percentage of individual improvements in the B and A2 phases at every time point were calculated and averaged. A value of $P < .05$ was considered statistically significant. Statistical analysis was performed with the SPSS software package. A change of more than 30% of an outcome measure was considered as clinically significant (minimal clinically important change [MCIC]).

3. Results

From January to December 2008, 20 patients (7 male/13 female; mean age 38.9 years, SD 14.1) with CRPS-1 according to the Bruehl and Harden/IASP criteria were consecutively enrolled in the study. Eleven patients had upper limb CRPS-1, and 9 patients had lower
limb CRPS-1. Specific characteristics of these patients are listed in Table 2. The average time between the inciting injury and the moment of study inclusion was 6.6 months (SD 4.1). Four patients with CRPS-1 of the lower limb used crutches. At the start of the study, all patients used analgesics combined with other CRPS-specific medication, and they all had physical therapy or occupational therapy within the borders of experienced pain according to the “with pain no gain” concept [24]. The CRPS-specific medication and adjuvant therapy used among the 20 included patients were acetaminophen \((n = 6)\), nonsteroidal anti-inflammatory drugs (NSAIDs; \(n = 10\)), opioids \((n = 6)\), anticonvulsants and tricyclic antidepressants \((n = 5)\), free-radical scavengers DMSO \((n = 3)\), acetylcysteine \((n = 4)\), mannitol \((n = 2)\), vasodilatory medication \((n = 5)\), transcutaneous electrical nerve stimulation (TENS; \(n = 3)\), and sympathetic blockades \((n = 4)\).

During the A1 phase, CRPS-specific medication and adjuvant therapies were reduced and finally stopped. In the A1 phase, the individual VAS pain scores varied to such an extent that it was not possible to detect a significant medication withdrawal effect. With the TSK score, it was found that 72% of the included patients believed that CRPS pain was a sign of ongoing injury and tissue damage and assumed that pain was a warning signal telling them to stop using their painful extremity in daily activities to prevent further injury.

One female patient (No. 20) with CRPS in the lower extremity withdrew from the study after the first PEPT session because she was not motivated to perform the proposed exercises. The decision was made before the first PEPT session and therefore was not a consequence of discomfort related to PEPT. Six patients underwent 6 PEPT sessions including follow-up. Fourteen patients achieved their predefined treatment goals before the maximum of 6 PEPT sessions; 7 patients had 5 sessions; 5 patients had 4 PEPT sessions; 2 patients had 3 PEPT sessions. Except for the patient who withdrew from the study in the A1 phase, there were no patients who discontinued the study because of discomfort or adverse effect related to PEPT treatment.

### Table 2. Patient characteristics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Duration between inciting event and inclusion (mo)</th>
<th>Inciting event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper extremity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>55</td>
<td>Female</td>
<td>4</td>
<td>Wrist fracture</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>Male</td>
<td>13</td>
<td>Wrist distorsion.</td>
</tr>
<tr>
<td>10</td>
<td>27</td>
<td>Male</td>
<td>6</td>
<td>Wrist contusion.</td>
</tr>
<tr>
<td>11</td>
<td>32</td>
<td>Female</td>
<td>6</td>
<td>Wrist operation</td>
</tr>
<tr>
<td>12</td>
<td>49</td>
<td>Female</td>
<td>7</td>
<td>CTS operation</td>
</tr>
<tr>
<td>13</td>
<td>35</td>
<td>Male</td>
<td>7</td>
<td>Extensor dig</td>
</tr>
<tr>
<td>15</td>
<td>48</td>
<td>Female</td>
<td>3</td>
<td>IV injury</td>
</tr>
<tr>
<td>16</td>
<td>41</td>
<td>Female</td>
<td>3</td>
<td>Metacarpal II fracture</td>
</tr>
<tr>
<td>17</td>
<td>29</td>
<td>Female</td>
<td>7</td>
<td>Hand contusion.</td>
</tr>
<tr>
<td>18</td>
<td>77</td>
<td>Female</td>
<td>3</td>
<td>Wrist distorsion</td>
</tr>
<tr>
<td>19</td>
<td>24</td>
<td>Female</td>
<td>13</td>
<td>Wrist distorsion</td>
</tr>
</tbody>
</table>

| Lower extremity |
|-----------------|----------------|
| 2               | 34 Male 3      |
| 4               | 47 Female 4    |
| 5               | 20 Female 5    |
| 6               | 31 Male 5      |
| 7               | 34 Female 3    |
| 8               | 44 Male 8      |
| 9               | 47 Male 18     |
| 14              | 19 Female 10   |
| 20              | 30 Female 3    |

CTS = carpal tunnel syndrome; MTP = metatarsophalangeal joint; Dig = digit.
3.6. Muscle strength

The baseline grip strength difference between sides was 23.6 N (SD 16.7), which was set to 100%. The baseline grip strength improved significantly to a smaller difference between sides by 52% to 11.5 N (SD 11.4; P < .001) during the A2 phase. The baseline plantar flexion strength side difference was 114.3 N (SD 96.5) (100%) and also improved significantly by 59% to 67.8 N (SD 68) during the A2 phase.

3.7. Arm activity

The average DASH scores were 71.7 (SD 16.2) at baseline and 45.7 (SD 18.2) in the A2 phase, which was a significant improvement of 36% (P < .001).

3.8. Walking capacity

During the baseline phase, 4 patients used crutches permanently. During the B phase, the use of crutches was reduced, and in the A2 phase, none of the patients used crutches at all. In the baseline A1 phase, the average 10-meter walking test was 18.8 s (SD 16.6), and the baseline timed up-and-go test was 14.4 s (SD 16.6). The 10-meter walking speed improved significantly by 29% from phase A1 to phase A2 (P = .002). The average 10-meter speed in A2 was 8.5 s (SD 5.2). The average timed up-and-go test in phase A2 was 7.2 s (SD 2.5), which is a significant improvement of 25% from phase A1 to phase A2 (P < .001).

3.9. Disability

In the baseline A1 phase, the average PDI was 37.8 points (SD 9.4), and it improved significantly by 60% to 15.3 points (SD 13.7) in the A2 phase (P < .001). In the A2 phase, 6 patients reported that their activities were no longer restricted by pain (PDI < 5). Five patients were slightly restricted (PDI between 5 and 20), and 8 patients still experienced serious pain-related disabilities (PDI > 20).

3.10. Kinesiophobia

The average score on the Tampa Scale of Kinesiophobia (TSK) was 22.7 (SD 5.5) in the A1 phase, and it decreased significantly by 18% to 18.7 (SD 6.5) in the A2 phase (P < .001).

3.11. Quality of life

During the A1 phase, the average general health perception score as part of patient quality of life was 62 (SD 16.3), and this general health perception score improved slightly to 68 (SD 16.4) (P = .07) during phase A2. The average perceived health change between phase A1 and phase A2 improved significantly by 269% (P < .001) from 27.6 (SD 21.3) in phase A1 to 74.3 (SD 21.7) in phase A2.
caused and often maintained to a substantial extent by the cognitions and behavior of doctors, therapists or partners who think and express that pain and other CRPS-1 symptoms are a sign of ongoing injury and tissue damage. Recommending the avoidance of painful activities may further induce an iatrogenic state of “learned disuse” [7,45].

Although randomized controlled trials with a sufficient sample size are necessary to address the natural course of CRPS and the efficacy of PEPT, we found indications that PEPT increased the level of activities measured by the PDI and DASH, walking measured by walking capacity tests and quality of life measured by the RAND SF-36. The suggested mechanism of action is that a progressive-loading exercise program with management of pain-avoidance behavior restores the impaired injury healing process, peripheral and central sensitization, local autonomic deregulation and cortical representation of the affected limb. PEPT is a comprehensive, inexpensive, noninvasive treatment that aims to counteract 2 possible maintenance factors of CRPS-1: pain avoidance and disuse. Pain avoidance (such as passive behavioral coping strategies of resting and retreating) is considered a maladaptive response to pain. Patients avoid physical and social activities that are expected to cause an increase in pain and suffering. In our study, it was found that 72% of the included patients assumed that pain was a warning signal telling them to stop using their painful extremity in daily activities to prevent further injury. In time, avoidance behavior and worrying/catastrophizing are assumed to lead to a considerable reduction in the level of physical and psychological functioning [32]. Their negative impact on the musculoskeletal and local vascular system may increase functional disability and undesirable physical consequences and may result in limited functioning. Theoretically, a direct link between psychological factors and CRPS is possible. Psychological factors such as emotional distress (eg, anxiety, anger, and depression) can be associated with increased catecholaminergic activity [12] and thus could in theory interact with adrenergic pathophysiologica mechanisms believed to contribute to CRPS [4]. Furthermore, chronic pain studies indicate that helplessness, fear of pain and passive pain coping strategies are all related to pain level [31]. Specifically in CRPS, it has been found that emotional arousal has a greater impact on pain intensity than in non-CRPS chronic pain [1]. Disuse and inactivity associated with pain-avoidance behavior are the suggested underlying and maintenance factors of dynamic changes in the cortical representations of the affected limb and may lead to autonomic deregulation and trophic changes in the affected limb [4,14]. Neuro-imaging studies in the early phase of CRPS-1 have shown a reduction in the size of the representation of the CRPS-affected limb in the somatosensory cortex compared to the unaffected side [17,19]. These changes appear to be reversible. Two studies indicate that these alterations return to normal after successful CRPS treatment [18,28]. Progressive-loading exercise programs are strong therapeutic interventions to counteract disuse of an extremity. For instance, constraint-induced movement therapy in stroke patients has shown that this intensive exercise program counters “learned” disuse, improves arm-hand function [38] and induces massive cortical reorganization in the brain [39]. In 1987, Watson and Carlson described the first active stress-loading program for patients with CRPS-1. With a progressive scrub and carry loading program, they reported an improvement in pain (65%), motion (65%) and grip strength (73%) in 41 patients with CRPS of the hand [47]. Two studies in children and adolescents (8–17 years of age) indicated that, in 60% to 95% of the participants, a complete recovery of symptoms occurred after intensive physical therapy and cognitive-behavioral treatment [16,34]. In a retrospective cohort study that included 106 adult patients with long-lasting CRPS-1, the function of the affected arm or leg improved in 95 patients. Full functional recovery was observed in 49 (46%), with a decrease in pain in 75 patients (71%) [9]. In 2005, Daly and Bialocerkowski [6] critically evaluated the evidence on the effectiveness of physical therapy to manage adult CRPS-1. They found that physical therapy treatments varied among studies and were often provided in combination with medical management that did not allow for the “stand-alone” value of physical therapy to be determined. Narrative synthesis of the results, based on effect size, found there was good to very good-quality level II evidence that graded motor imagery is effective in reducing pain in adults with CRPS-1 [7]. Evidence for the efficacy of physical and occupational therapy in combination with pharmacotherapeutic treatment of CRPS was found in 2 randomized studies. In these studies, evidence was found for the efficacy of the so-called pain contingent physical and occupational therapy, which is therapy within certain pain limits, focusing mainly on compensational methods to help patients cope with their limitations [24,25]. Recently, Stanton-Hicks [35] reported preliminary results on the effi-
cacy of a 3-week exercise program, with emphasis on behavioral and psychological management, in 69 children and adolescents with CRPS-1. With this program, the author found a 51% improvement in pain severity and 62% improvement in physical functioning. In summary, these and our data indicate that exercise programs despite pain, with a focus on normal activity and participation, may be effective. The added value of PEPT is that pain relief and complete remission of CRPS symptoms can be reached without specific CRPS medication and/or other invasive treatments.

A limitation of this study is the relatively small number of included patients. The study was designed as a preliminary study for a controlled randomized trial and was necessary to determine possible harmful side effects. Because the current standard among many physicians and physical therapists treating CRPS used loading exercises under the “with pain, no gain” concept, this study was a prerequisite for larger trials. Even with the restricted number of included patients, the study was able to demonstrate that no harmful side effects exist, and the power was sufficient to demonstrate that most treatment effects are clinically relevant (MCIC > 30%) and some treatment effects are statistically significant. The clinical implication of this study is that PEPT may now be performed without restrictions with respect to safety. Further randomized clinical trials are necessary to demonstrate the superiority of PEPT to existing treatment strategies.

Conflict of interest statement
The authors have no conflict of interest.

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