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Review Article

Harmful or safe? Exposure and pain provocation during physiotherapy of complex regional pain syndrome I: a narrative review

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Abstract.
BACKGROUND: Complex regional pain syndrome (CRPS) is a clinical diagnosis and an umbrella term for a heterogeneous group of states associated with pain disproportionate to any inciting event, together with a number of signs and symptoms that are manifested mainly in the limbs. There are often concerns among clinicians and patients about the potential harms caused by pain provocation during physiotherapy of CRPS, even though clinical guidelines de-emphasize pain-contingency.
OBJECTIVE: The objective of this narrative review is to summarize current evidence regarding potential harms due to pain provocation during so-called exposure-based therapies in individuals with CRPS.
METHODS: Six studies evaluating exposure-based approach were included ($n = 6$).
RESULTS: Although only one included study focused primarily on safety and in the rest of the included studies the reporting of harms was insufficient and therefore our certainty in evidence is very low, taken together with outcome measures, available data does not point to any long-term deterioration in symptoms or function, or any major harms associated with pain provocation during physiotherapy of CRPS.
CONCLUSION: There is a great need for higher-quality studies to determine which therapeutic approach is the most appropriate for whom and to evaluate the risks and benefits of different approaches in more detail.

Keywords: Complex regional pain syndrome, rehabilitation, risk assessment, safety, adverse effects, exposure therapy

1. Introduction

Complex regional pain syndrome (CRPS) is a pain syndrome that can develop after trauma, surgery, immobilization, minimal injuries and possibly even spontaneously [1–3]. CRPS has also been associated with soft-tissue injuries to the shoulder after a stroke [4]. A typical feature of CRPS is pain disproportionate to any inciting event and that CRPS primarily affects the limbs. Further, although the pain is often described with characteristics typical of neuropathic pain, peripheral nerve lesions have typically not been proven in type I CRPS [1–4]. CRPS is a clinical diagnosis with a controversial history that covers a relatively heterogeneous group of clinical manifestations with not fully explained etiopathogenesis [5,6]. CRPS is now predominately being associated with functional and structural changes in the neurological and immune systems, however, the results of different authors are often contradictory [7–18]. Currently, the Budapest Criteria are used in the diagnosis of CRPS [1], which are described in Table 1. Differential diagnosis is paramount since CRPS is a diagnosis based on exclusion [1,19]. For this reason, additional assessment methods facilitating diagnosis and

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Table 1
Budapest criteria

Conditions	Continuing pain which is disproportionate to any inciting event	The patient has at least one sign in two or more of the categories	The patient reports at least one sign in three or more of the categories	No other diagnosis can better explain the signs and symptoms
Categories	**Sensory:** hyperalgesia and/or allodynia	**Vasomotor:** temperature asymmetry and/or skin colour changes and/or skin colour asymmetry	**Sudomotor/oedema:** oedema and/or sweating changes and/or sweating asymmetry	**Motor/trophic:** decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

treatment incl. diagnostic imaging should be used in selected patients [1,5,7]. Regarding prognosis, recent prospective study shows that only 5.5% of individuals with CRPS are asymptomatic 12 months after the onset even with treatment, although the majority showed significant improvements in pain (average decrease of 50%) and disability (average decrease of 60%) [20]. Unfortunately, it seems that in a minority of individuals with CRPS symptoms persist or even worsen and progress over time [21].

There is generally a lack of robust evidence for the use of any physiotherapy management approach and for this reason, existing management strategies are mostly based only on insufficient evidence or expert opinions while the mechanism of action is not fully understood [22–25]. According to clinical practice guidelines [1,19,26,27], early diagnosis and timely treatment are paramount and patients must have access to rehabilitation treatment as soon as possible. There is also consensus that physiotherapy should be goal-oriented and focus should be placed on restoration or preservation of function as well as on pain management. Earlier guidelines promote pain-contingency [26] while more recent guidelines de-emphasize a pain-contingent approach and point out that therapy should be graded and function-oriented while an optimal balance between "doing too much" or "doing too little" must be sought [1,19,27]. There is an ongoing debate whether a reduction in pain facilitates an increase in function or an increase in a function facilitates pain reduction or when one is more important than the other. Because of this, there is a spectrum of opinions regarding the balance between these seemingly contradictory approaches [28]. Unfortunately, there is huge uncertainty involved as there is no evidence to guide us in the exact dosing, intensity, order or a suitable combination of approaches, nor to tell us who will respond better to which regimen. In summary, it can be recommended that "(1) no single-treatment approach should be preferred for management of this client group and (2) therapists should not blindly apply all treatment approaches" [29].

1.1. Pain provocation during exposure-based therapies

Exposure-based approaches were developed due to the perceived insufficient effects of the commonly used interventions for some individuals with CRPS. It is hypothesized that too much emphasis on pain control could adversely affect the quality of life, disability and paradoxically also pain through intertwined psychological (e.g. pain-related fears), behavioural (e.g. avoidance) and physiological factors (changes in peripheral tissues as well as functional and structural changes of the neuro-immune system) [30,31]. The goal of exposure-based approaches is primarily to reduce avoidance behaviours and increase function to which pain is secondary. There is some evidence that the perceived harmfulness of activities mediates disability in chronic CRPS [32] but kinesiophobia, fear-avoidance and pain catastrophizing are not mediators for disability or pain when measured via questionnaire [32,33]. Thus, reducing the avoidance and perceived harmfulness of activities would seem to be potential treatment goals. These approaches have in common a thorough individualized education and motivation of individuals with CRPS and the creation of appropriate conditions to increase the levels of activity – especially towards pre-defined and individually valuable and meaningful activities. Exposure outside the therapy is also encouraged and independence from the therapist is gradually promoted. Parallels with exposure-based approaches, e.g. graded activity and graded exposure in vivo, in chronic low back pain patients are apparent [34,35].

Graded Exposure in vivo (GEXP) in the context of CRPS treatment was first described by de Jong et al. [30] and was created especially for individuals with increased fear of movement and re/injury. Education in GEXP focuses on the hypothesized vicious circle of pain $>$ fear $>$ avoidance $>$ disability $>$ pain with the major goal to increase the willingness to engage in activities and situations that patients have been avoiding. In GEXP, a hierarchy of activities according to the levels of concern about them is used and individuals are instructed to engage in these fearful activities and

sensations as much as possible until anxiety levels decrease with the notion "no pain, no gain" [30,36]. Pain Exposure Physical Therapy (PEPT) was described first by Ek et al. [31] and does not target individuals with increased fear specifically. Education in PEPT includes framing pain as a "false warning sign" and "reversible dysregulation of the nervous system" and it is emphasized that although short-term worsening of some CRPS symptoms is likely during or after therapy it is not a sign of harm or a reason to reduce activity or intensity of the exercise [31]. PEPT consists of progressive-loading exercises and desensitization beyond the patients' pain limits [37] and explicit instruction to ignore the pain is given as well as information that therapists will not respond to any pain reports [31]. PEPT includes also passive approaches to increase the range of motion, strength and function, incl. manual techniques. Further, the PEPT programme involves partners and family members, is led by two therapists at the same time and all medication is ceased [31].

Other approaches additionally include exposure. Graded Motor Imagery (GMI) is basically graded exposure and incorporates some elements of the aforementioned approaches, but is based on a somewhat different rationale and has some important specifics incl. limitation of pain increases during exposure with the goal of "disassociating movement and pain" [38]. Thus, GMI will not be the main focus of this narrative review. In the past so-called "stress-loading" was developed by Watson and Carlson [39]. This consists of exposure to active traction and compression exercises that provide stressful stimuli to the extremity without joint motion. Because their study was aimed at individuals with "reflex sympathetic dystrophy" and the current CRPS diagnostic criteria were not used at that time, stress-loading will not be evaluated further in this review.

2. Objectives

Even though clinical practice guidelines de-emphasize pain contingency [1,19,27] and there is some evidence that exposure-based approaches and desensitization are being implemented in clinical practice [40–43], pain aggravation during physiotherapy of individuals with CRPS is commonly perceived as dangerous by clinicians [43] and patients. This could be problematic because it is hypothesized that increased pain-related fear resulting in excessive focus on pain control and any associated avoidance of activity perpetuates a vicious cycle leading to more disability and pain [33,37]. Since pain provocation during movement or exercise is standardized in the form of exposure to valued but painful activities in the so-called exposure-based approaches, results of studies regarding exposure-based approaches could be used as a proxy for evaluation, whether or not pain provocation during movement is harmful for individuals living with CRPS. Thus, the main objective of this narrative review is to answer the following PICO question [44]: Are exposure-based approaches associated with any harms in adult individuals diagnosed with CRPS? A related secondary goal was to also evaluate to what extent and quality are harms reported in studies regarding exposure-based therapies.

3. Methods

This narrative review was conducted in accordance with a Scale for the Quality Assessment of Narrative Review Articles (SANRA) [45] and secondarily with the PRISMA harms checklist [46] since its focus is on harms. This study, as a literature review, is exempt from Institutional Review Board approval. The main author identified articles using keyword database searches and then by a manual search through reference lists of identified eligible studies. Eligibility criteria were based on a PICO(S) format suggested by PRISMA statements [44]:

- Population: adult individuals diagnosed with CRPS
- Intervention: exposure-based approach as a primary intervention
- Outcomes: adverse events reports and/or outcome data for disability and/or pain
- Study type: any prospective interventional study design with any length of follow-up

Further, only studies written in English were eligible and this review searched only for published data. Exposure-based approaches were defined as any approach where a) exposure to painful activities or exercises is explicitly implemented and promoted, b) pain-contingency is de-emphasized and c) where pain provocation or aggravation is not a signal to cease the intervention. For this review, we followed the definition of harms by CONSORT extension [47] defining harms as "the totality of possible adverse consequences of an intervention or therapy". Specifically, this review was focused on a) any reported adverse events, b) any reported deterioration in functional state and c) any reported long-term increase in pain intensity ($>$ 1.5/10 increase at follow-ups [48,49]). Since adverse events

Table 2
Search strategy

PubMed: (("CRPS"[All Fields] OR ("complex regional pain syndromes"[MeSH Terms] OR ("complex"[All Fields] AND "regional"[All Fields] AND "pain"[All Fields] AND "syndromes"[All Fields]) OR "complex regional pain syndromes"[All Fields] OR ("complex"[All Fields] AND "regional"[All Fields] AND "pain"[All Fields] AND "syndrome"[All Fields]) OR "complex regional pain syndrome"[All Fields])) AND ("exposure"[All Fields] OR "exposure s"[All Fields] OR "exposured"[All Fields] OR "exposures"[All Fields] OR "exposuring"[All Fields])) AND ((casereports[Filter] OR clinicalstudy[Filter] OR clinicaltrial[Filter] OR controlledclinicaltrial[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]) AND (humans[Filter]) AND (english[Filter]))
Cochrane Library: (complex regional pain syndrome): ti, ab, kw AND (exposure): ti, ab, kw
PEDro: Abstract & Title field: complex (AND) regional (AND) pain (AND) syndrome (AND) exposure
Web of Science: complex regional pain syndrome (Abstract) and exposure (Abstract)

and deterioration in functional state or long-term increase in pain intensity could be reported also in studies primarily focused on efficacy, these studies were included as well as studies focusing primarily on harms. This discrepancy between primary and secondary study goals will be distinguished in the results section.

PubMed, Cochrane Library, PEDro and Web of Science databases were searched using the terms 'complex regional pain syndrome' and 'exposure' from inception to January 2022. The last search was performed in July 2022. The search strategy is described in Table 2. The records located were screened for relevance by title. Duplicates and not relevant records were removed. After that, the identified reports were retrieved and assessed for eligibility. Further, reference lists of these reports were screened for additional studies. The main author extracted the following relevant data from each eligible study: first author and year of publication, study design and setting, intervention description, characteristics of participants, duration of follow-up, outcome measures (pain, disability, quality of life), medication use, dropouts and adverse events reports. Since the aim of this narrative review was not to evaluate the effectiveness of exposure-based approaches over other therapies but only associated harms and their safety, an extension of the CONSORT statement for reporting harms [47] was used for all included studies. Even though CONSORT harms extension was developed for evaluation of randomized clinical trials, it was also used for any prospective interventional study included in this review, as it was used by some authors for evaluation of observational studies previously [50,51]. Further, to summarize to what extent the harms are reported overall in the studies regarding exposure-based approaches, CONSORT harms extension [47] was used also for studies primarily investigating efficacy, despite of being intended for studies primarily investigating harms. Both these discrepancies will be distinguished in the results section.

4. Results

A total of 107 records were identified through the search. Duplicates ($n = 32$) and not relevant records ($n = 57$) were removed. After an assessment of the eligibility of the retrieved reports, twelve were removed ($n = 12$) and six articles meeting the inclusion criteria were included [30,31,36,37,52,53]. Thus, the total number of included studies was six ($n = 6$) with 201 participants in single-case experimental studies and randomized controlled trials (those allocated in exposure treatment arms). Figure 1 presents this process in more detail.

Only one study reported "safety" as a primary goal [37] and one study reported "efficacy and safety" as a primary goals but focused on efficacy only [31]. Only two identified studies were randomized controlled trials [36,52]. Regarding adverse events associated with PEPT and its safety, van de Meent et al. [37] actively collected data about the severity of predefined CRPS signs and symptoms as well as functioning and disability 3–4 times per treatment phase and specified that a 30% change was determined as a minimal clinically important change (MCID), but no grading was implemented. Even though described, fluctuations in symptoms on an individual level were unfortunately not numerically presented and only some measurement methods were previously validated. Further, Barnhoorn et al. [52] stated that serious adverse events during PEPT treatment were collected through the use of a standardized form, but without sufficient details – in the trial protocol [54] it was found that exacerbations of signs and symptoms leading to medical consultation were monitored with this form but it was not clear whether an active or passive approach was implemented. Two other studies mentioned the absence of adverse events or harms but did not specify anything about their collection or interpretation [31,36]. It can be speculated that in these studies the absence of adverse events or safety was referring to disability and pain outcomes but

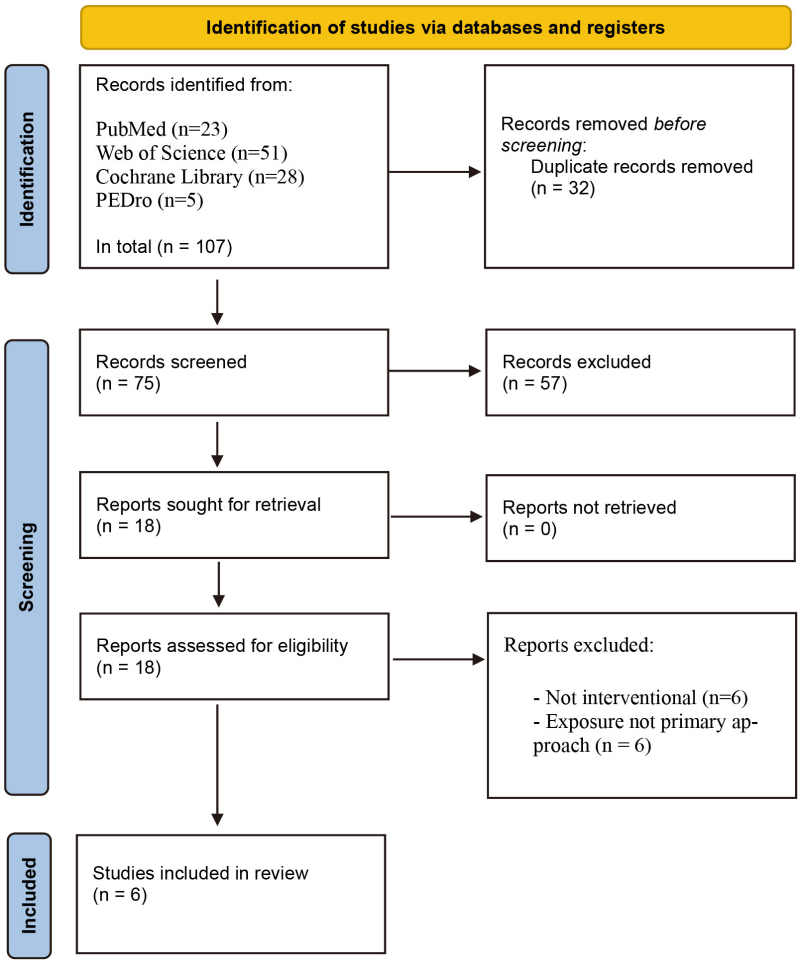

Fig. 1. Flow diagram.

this was not explicitly specified and necessary details were lacking. Further, in two studies adverse events or harms were not mentioned at all [30,53]. No study specified how severity or seriousness was measured nor whether and how causality was assessed or determined. On the other hand, all the included studies provided sufficient descriptions of withdrawals that were due to harm and the experience of the allocated treatment. Although drop-out rates were significant (25 out of 201, i.e. 12%), most of them occurred prior to the treatment or after education about the treatment ($n = 14$ (7%)) or were not adversely related to the treatment ($n = 5$ (2.5%)). Only four participants withdrew during the treatment period (PEPT) specifically for the reason that the intervention was too painful and strenuous ($n = 4$ (2%)) and two were lost to follow-up without any given reason ($n = 2$ (1%)). In the only study investigating "safety" as a primary goal, which was of multiple single-case design [37], the quality of reporting of harms based on the 10-items of extended CONSORT criteria [47] was sufficient (9/10). In the other included studies [30,31,36,52,53] without this primary aim the quality of reporting of harms [47] was clearly insufficient or absent (1–4/10). Details can be found in Table 3.

Follow-ups in the included studies ranged between 2–9 months and the mode was 6 months. Although fluctuation of symptoms during the intervention phase as well as a temporary increase in pain and other symptoms during and after physiotherapy sessions were common, this was expected and explained to patients. No study reported any long-lasting increase in symptoms or deterioration of function at follow-up. It is of interest, that all the included studies that presented numerical data for pain intensity (sample means) [31,36,37,52] reported a decrease in pain at follow-up which was clinically significant, despite the fact that pain reduction was not the main aim of these approaches. Of interest is also the

Table 3
Extended CONSORT criteria – quality of reporting of harms [47]

	van de Meent et al. [37] (†)	Barnhoorn et al. [52] (*‡)	Ek et al. [31] (‡)	den Hollander et al. [36] (*‡)	de Jong et al. [30] (§)	den Hollander et al. [53] (§)	
1. If the study collected data on harms and benefits, the title or abstract should so state.	+	−	+	−	/	/	2/6
2. If the trial addresses both harms and benefits, the introduction should so state.	+	−	+	−	/	/	2/6
3. List addressed adverse events with definitions for each.	++	−	−	−	/	/	1/6
4. Clarify how harms-related outcomes were collected.	++	+	−	−	/	/	2/6
5. Describe plans for presenting and analyzing information on harms.	++	−	−	−	/	/	1/6
6. Describe for each treatment arm the participant withdrawals that are due to harms and the experience with the allocated treatment.	++	++	++	++	++	++	6/6
7. Provide the denominators for analyses on harm.	+	−	−	−	/	/	1/6
8. Present the absolute risk of each adverse event and present appropriate metrics for recurrent events, continuous variables and scale variables, whenever pertinent.	+	−	−	−	/	/	1/6
9. Describe any subgroup analyses and exploratory analyses for harms.	−	−	−	−	/	/	0/6
10. Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability, and other sources of information.	++	++	++	−	/	/	3/6
	9/10	3/10	4/10	1/10	1/10	1/10	

*Randomized controlled trial, † “safety” as primary goal, ‡ adverse events as secondary findings, § adverse events/harms not mentioned. “−” not fulfilled or not mentioned; “+” partially fulfilled; “++” fulfilled, “/” not applicable.

Table 4
Summary of Pain Exposure Physical Therapy (PEPT) studies

Authors	Study design and setting	Intervention	Sample characteristics	Outcomes	Drop-outs	Deterioration/adverse events
Ek et al. [31]	Prospective description of a case series Setting: not-specified outpatient clinic	– Education, active and passive interventions aimed at maximal function, instructions to ignore pain and that therapists will not react to pain; all other treatments incl. medication were stopped. – Maximum of 5 sessions in 3 months.	($n = 106$) – Average age 45 years. – Average duration of symptoms 4.6 years. – Average pain at baseline 4.9/10 (VAS)	– Follow-up at 3–4 months – 74% reported decrease in pain intensity; 90% reported increase in function. – Pain (VAS) decreased on average by 2.2 points (45%); RST-lim decreased on average by 15.2 points (72%) and walking duration by 51 minutes (538%).	– **Withdrew during the treatment:** ($n = 4$): intervention being too strenuous and too painful. – **Lost to follow-up:** ($n = 2$): without given reason. – **Withdrew in total:** 6 (6%)	– Temporary increase in pain and swelling following the session was common and 14 (14%) reported higher pain after treatment; no patient showed a long-lasting increase in symptoms or functional deterioration at follow-up. – No other adverse effect was noted in any patient. – *It was not specified how adverse events reports were collected.*
Van de Meent et al. [37]	Multiple single-case design Setting: rehabilitation department with CRPS specialization, delivered by two therapists	– Same as Ek et al. [31] – Maximum of 6 sessions in 3 months.	($n = 20$) – Average age 39 years. – Average duration of symptoms 0.6 years. – Average pain at baseline 58/100 (VAS).	– Follow-up at 2 months – Pain (VAS) decreased on average by 33/100 points (57%); PDI on average by 22.2 points (60%); SF-36-PHC increased on average by 46.7 points (170%) – 14 (70%) achieved their predefined treatment goals	– **Withdrew prior the treatment:** ($n = 1$): not motivated to perform proposed exercises. – **Withdrew in total:** 1 (5%)	– Pain and disability levels fluctuated during the intervention period and three patients initially showed increased vegetative signs, but no long-term increase in CRPS symptoms occurred. – No patients discontinued the treatment because of discomfort or adverse effects and no harmful side effects were reported. – *Standardized measurements of CRPS signs and symptoms were subsequently taken 3–4 times per study phase (MCID 30%).*
Barnhoorn et al. [52]	Randomized controlled trial Setting: rehabilitation department with CRPS specialization, delivered by two physical therapists trained by a psychologist	– PEPT: Same as Ek et al. [31], although $n = 10$ (36%) received some form of medication or other conventional treatment; average number of sessions was 4. – CONT: "pain-contingent" physiotherapy following the Dutch guidelines (Perez et al. [26]) and prescribed medication; average number of sessions was 17.	($n = 56$) – Average age 44 years. – Average duration of symptoms 0.5 years. – Average pain at baseline 6.7/10 (VAS).	– Follow-up at 9 months – PEPT: ISS-RV decreased on average by 6.7/40 points (32%) and 63% reached MCID (4 points); pain (VAS) decreased on average by 2.7/10 points (43%); PDI on average by 21.6 points (60%); SF-36 increased on average by 23 points (52%). – There was no significant difference in intention-to-treat analysis between groups (in per-protocol analysis PEPT group had more favourable outcomes).	– **Switched prior the treatment:** PEPT to CONT ($n = 4$); CONT to PEPT ($n = 11$). – **Switched during the treatment:** CONT to PEPT ($n = 3$): insufficient results. – **Lost to follow-up:** PEPT ($n = 1$): complete recovery; CONT ($n = 2$): lack of confidence about the treatment or without offering a reason. – **Withdrew or switched in total:** PEPT 5 (18%); CONT 16 (57%).	– In PEPT no long-term deterioration or serious adverse events were reported; In CONT only transient non-severe adverse events occurred due to medication. – 75% in the PEPT and 73% in CONT reported therapy as feasible. – *Standardized serious adverse event form was used (exacerbations of signs and symptoms leading to medical consultation) and side effects were documented in the patient's medical record.*

CONT – control group; ISS-RV – Impairment level Sum Score-Restricted Version; MCID – Minimal Clinically Important Change; PDI – Pain Disability Index; PEPT – Pain Exposure Physical Therapy; RST-lim – Radboud Skills Test limitation score; SF-36-PHC – 36-Item Short Form Survey-physical health component; VAS – Visual Analogue Scale.

Table 5
Summary of Graded Exposure in vivo (GEXP) studies

Authors	Study design and setting	Intervention	Sample characteristics	Outcomes	Drop-outs	Deterioration/adverse events
de Jong et al. [32]	Single-case experimental design Setting: secondary care; experienced behavioural therapist, supervised by a rehabilitation specialist	– Education and exposure to hierarchy of feared activities in patients with increased fear of movement and re/injury aimed at maximal function. – Duration of 20 hours in 10 weeks.	($n = 8$) – Average age 40 years. – Average duration of symptoms 3 years. – Average pain at baseline is not numerically presented (in graphs).	– Follow-up at 6 months – Pain (VAS) decreased and the performance of personal relevant activities increased in all participants but exact values are not presented (graphs); – WSQ/QRS decreased to 0 (no functional disability) in all 3 lower limb patients; RASQ decreased on average by 25.4 points (65%) in 5 upper limb patients; disability decreased by at least 50% in all subjects. – Other subjective CRPS symptoms were not present at follow-up in any patients.	– No patient withdrew.	– Self-report (dichotomous) about CRPS signs and symptoms before and after each intervention and at follow-up, diary (pain, activities performance). – Pain and disability levels fluctuated during the intervention period (*estimated from the graphs*), but all the patients reported a positive change in CRPS-related signs and symptoms and disability at follow-up. – It was not specified whether and how adverse events reports were collected
den Hollander et al. [36]	Randomized controlled trial Setting: tertiary care centre, experienced GEXP therapists	– GEXP: Same as de Jong et al. [30] but $n = 15$ (65%) were using medication. – CONT: "pain-contingent", local rest, connective tissue massage, pain reducing exercise, compensatory activities, TENS. – Both groups had 17 sessions (1 hour) in 17 weeks.	($n = 46$) – Average age 45 years. – Average duration of symptoms 5 years. – Average pain at baseline 5.5 (NPS).	– Follow-up at 6 months – GEXP: Pain (NPS) decreased on average by 2.6 points (47%); RASQ decreased on average by 1.27 points (40%) in upper limp patients, WAQ decreased on average by 5.4 points (78%) in lower limp patients; SF-36-PC increased on average by 26.2 points (66%). – Results favoured GEXP group, which showed clinically and statistically significant difference.	– **Withdrew before the treatment/after education:** GEXP ($n = 3$): schedule was inconvenient; treatment too psychological; other goals. CONT ($n = 2$): schedule was inconvenient; without given reason. – **Withdrew during the treatment:** GEXP ($n = 2$): legal problems; considered herself recovered. CONT ($n = 4$): three were disappointed; one recovering from cardiac surgery. – **Withdrew in total:** GEXP 5 (22%); CONT 6 (26%). – **Switched groups after follow-up:** from GEXP 0 (0%); from CONT 6 (35%).	– No adverse events occurred in any group – *It was not specified how adverse events reports were collected.*
den Hollander et al. [53]	Replicated single-case experimental design Setting: outpatient rehabilitation department, behavioural therapist and an occupational therapist experienced in the cognitive behavioural rehabilitation	– Same as de Jong et al. [30] – 18 sessions (1 hour) in 3 months. – mGEXP: exposed only once to 15 activities. – rGEXP: exposed repeatedly to 3 activities.	($n = 8$) – Average age 44.2 years. – Average duration of symptoms 3.5 years. – Average pain at baseline was not presented.	– 6 month follow-up. – mGEXP: This group showed statistically significant improvement in pain experience and disability after treatment and at follow-up. – rGEXP: This group showed statistically significant improvement only in disability after treatment and at follow-up.	– **Withdrew before the treatment/after education:** ($n = 2$): refused to terminate ongoing treatment; ($n = 4$): pain reduction was their only goal. – **Withdrew during the treatment:** ($n = 2$): diagnosed hearth problem; escalating family conflict. – **Withdrew after the treatment:** ($n = 2$): excluded for concealed involvement in a litigation procedure. – **Withdrew in total:** 8 (50%). *Drop-outs were replaced by new consecutive patient.*	– mGEXP ($n = 1$): decreased performance in one activity after treatment, but positive change relative to baseline at follow-up. – rGEXP ($n = 1$): large effect for TSK/PCS between baseline and post-treatment but deteriorated compared to baseline at follow-up. – No deterioration in pain experience or performance was reported in any group at follow-up. – *It was not specified whether and how adverse events reports were collected.*

CONT – control group; GEXP – Graded Exposure in vivo (m-multiple, r-repeated); NPS – Neuropathic Pain Scale; PCS – Pain Catastrophizing Scale; QRS – Questionnaire Rising and Sitting down; RASQ – Radbound Skills Questionnaire; SF-36-PC – 36-Item Short Form Survey-Physical Component; TSK – Tampa Scale of Kinesiophobia; TENS – Transcutaneous Electric Neural Stimulation; VAS – Visual Analogue Scale; WAQ – Walking Ability Questionnaire; WSQ – Walking Stairs Questionnaire.

observation that positive change in symptoms and function is more pronounced with longer follow-up after the treatment phase [30,36,37,52] which indicates that the effects of exposure-based therapies seem rather to increase over time and that early short-term increases in symptoms can precede improvement in some patients. It should be noted, however, that in both included RCTs medication was used together with the exposure-based approach in some patients (36% in PEPT [52] and 65% in GEXP [36]). In the other two included PEPT studies no report on adherence with medication cessation was present and in the other two included GEXP studies no mention of medication use was found.

Taken together, no adverse events were reported outside temporary fluctuations in CRPS-related symptoms but which were regarded as expected non-harmful side-effects. No withdrawals due to pain increase were reported during the treatment for GEXP and only 2% for PEPT. Summary of extracted data can be found in Tables 4 and 5.

5. Discussion

Even though only one included study evaluated "safety" as its primary goal and the reporting of harms in the rest of the included studies was of insufficient quality or absent, taken together with outcome measures, the available data does not point to any major adverse reactions by way of pain provocation during physiotherapy of individuals with CRPS outside of temporary increases in CRPS-related symptoms during the treatment period. But it has to be emphasized that absence of evidence should not be interpreted as evidence of absence, since only very few relevant studies were identified and only one focused primarily on safety. This insufficiency in harms reporting is surprising since these exposure-based approaches are not widely accepted [43]. But the included studies are not an exception, since a recent Cochrane review [22] reports that most studies regarding physiotherapy for CRPS did not report on adverse events and generally we are uncertain if any of the physiotherapy treatments investigated in the Cochrane review of RCTs (including PEPT [52] a GEXP [36]) caused any unwanted side effects [22]. For this reason, comparison with other approaches is not possible. But inadequate reporting of harms is generally problematic across clinical areas and types of interventions [55,56].

It should be emphasized that the results of this review must not be generalized to any pain provocation in CRPS patients. For example, even though based mainly on expert opinion for lack of robust evidence, elective surgery is recommended to be performed no less than 12 months after symptoms have settled or at least after the symptoms are well controlled because of the expected risk of exacerbation or recurrence of CRPS [57–59]. In cases when surgery is indicated, careful patient selection and appropriate pre-, peri- and post-operative management may lower this risk, but a number of the presented studies used older diagnostic criteria or combined CRPS types I and II [60–63].

What needs consideration is that drop-out rates indicate that $\sim$10% of participants were not willing to participate or complete these treatments due to treatment characteristics, but only 2% withdrew during the treatment phase from the seemingly more aggressive PEPT because of the intervention being too painful. This indicates that the majority of patients motivated enough to initiate participation in these exposure-based treatments tolerated temporary fluctuations in symptoms and were able to perform the proposed exercises. Drop-outs during exposure-based treatments are not an exception limited to CRPS – e.g. in low back pain trial with exposure [64] it was reported that 16% of participants withdrew during the exposure treatment period for reasons related to treatment, which is even a higher rate.

For future research, it should be recommended that reporting of harms and data about symptom fluctuation should be of higher quality and detail. Open or semi-structured questions may provide additional information about both expected and unexpected adverse events and harms. Also, reporting of psychological impact outside pain-related fears might be valuable as well (distress, anxiety, depression, etc.). Even though not based on any evidence, some authors argue that only activities in the full control of CRPS patients should be implemented because of the potential for psychologically traumatizing events due to insensitive handling or interventions against the will of the individual with CRPS [65]. Higher quality of harm reporting should lead to more realistic expectations and set boundaries about what is a common and normal reaction to these approaches and how to prevent any unintended harms. In terms of treatment effectiveness, comparison is also not possible since only two of the involved studies were RCTs and there are some methodological concerns in both of them [66]. Generally, there is a lack of higher-quality evidence to inform clinical decision-making [22,29].

6. Limitations

The main limitation of this narrative review is that available evidence is sparse and generally of low quality – only one identified study evaluated "safety" as the primary goal. Further, in almost all the included studies the treatment was delivered in a CRPS-specialized setting and/or by specifically trained therapist, which decreases any external validity for common practice. A significant risk for bias is that evaluation based on extended CONSORT criteria for reporting of harms [47] was performed by only one author. This is of importance because the subjective nature of assessment of harms reporting (e.g. multiple components in only one item) probably causes inconsistencies in assessments across assessors and reviews [55,56]. Further, even though the Scale for the Quality Assessment of Narrative Review Articles (SANRA) [45] was followed, narrative reviews are generally more prone to bias than systematic reviews, but for which significant resources are necessary.

7. Conclusion

Even though only very few relevant studies were identified and the reporting of harms in the included studies was generally of insufficient quality and therefore our confidence in the evidence is very low, taken together with outcome measures, available data does not point to any major harms associated with exposure-based approaches and related pain provocation during physiotherapy of CRPS. No deterioration in symptoms or function was reported at follow-ups and the majority of patients motivated enough to initiate participation in these pain-provoking treatments were able to perform the proposed exercises despite temporary fluctuations in CRPS-related symptoms. Comparison with other approaches is not possible since harms reporting is generally lacking and therefore should be a priority in future research.

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Conflict of interest

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