What is the landscape of evidence about the safety of physical agents used in physical medicine and rehabilitation? A scoping review

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ABSTRACT

Background Several systematic reviews (SRs) assessing the effectiveness of superficial physical agents have been published, but the evidence about their safety remains controversial.

Objective To identify areas where there is evidence of the safety of physical agents by a scoping review.

Design Four databases were systematically searched for including English SRs that explored and reported safety in terms of adverse events (AEs) related to the application of physical agents in outpatient and inpatient physical medicine and rehabilitation settings managed by healthcare professionals, published in January 2011–September 2021. The severity of AEs was classified according to the Common Terminology Criteria. Then, AE findings were summarised according to the SR syntheses. Finally, the reporting of the certainty of the evidence was mapped.

Results Overall, 117 SRs were retrieved. Most of the SRs included randomised controlled trials (77%) and patients with musculoskeletal disorders (67%). The most investigated physical agents were extracorporeal shock wave therapy (ESWT) (15%), transcutaneous electrical nerve stimulation (13%) and electrical stimulation (12%). No AE (35%) was reported in one-third of the included primary studies in SRs, whereas few severe AEs occurred in less than 1% of the sample. Among physical agents, ESWT showed an increased risk of experiencing mild AEs compared with the control. Most SRs reported a qualitative AE synthesis (65.8%), and few reported the certainty of the evidence (17.9%), which was mainly low.

Conclusion We found evidence of safety on several physical agents coming mostly from qualitative synthesis. No significant harms of these interventions were found except for ESWT reporting mild AEs. More attention to the AEs reporting and their classification should be pursued to analyse them and assess the certainty of evidence quantitatively.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This scoping review mapped the landscape of evidence about safety of a wide range of physical agents used in different areas of physical medicine and rehabilitation.

⇒ It was conducted following the framework recommended by the Joanna Briggs Institute methodology and reported according to the most current Preferred Reporting Items for Systematic Reviews and Meta-Analyses scoping review guidelines.

⇒ We included 117 systematic reviews using comprehensive literature searches in four databases.

⇒ We included only English systematic reviews published in the last 10 years.

INTRODUCTION

Clinicians generally apply physical agents to assist patients in their physical medicine and rehabilitation programmes to reduce inflammation, pain and motion restrictions.

Physical agents include heat, cold, water, pressure, sound, electromagnetic radiation and electrical currents. Healthcare professionals who directly apply physical agents to the skin should be aware of their safety or harm. As in pharmacology, the safety of interventions should also be assessed in physical medicine and rehabilitation. Moreover, patients should be informed of rare serious adverse events (AEs) and more common mild AEs (eg, bruising, muscle soreness) in patient-centred care. An available guideline to guide clinical decision-making for safe practice was published in 2010 by a team of physiotherapists in Canada, describing contraindications and precautions in the use of the six most commonly used electrophysical agents: cryotherapy, superficial thermal agents, electrical stimulation, low-level laser therapy (LLLT), short-wave diathermy (SWD) and therapeutic ultrasound. However, this guideline was not devolved through a rigorous systematic review (SR), and not all existing physical agents were assessed.

More recently, several SRs have been published about the effectiveness of physical...
agents, but the evidence about their safety remains controversial.

A significant way to assess safety is by reporting any AEs that arise during trials. Trial investigators can use active monitoring (eg, recording predefined AEs already known to be associated with an intervention) or spontaneous report monitoring (eg, recording all predefined or not predefined AEs, covering new or unexpected AEs) to collect intentionally solicited or unsolicited AEs.

Exploring the existing literature will increase awareness of the reporting and the occurrence of any AEs related to applying physical agents. Therefore, we aimed to map the landscape of evidence about the safety of physical agents used in physical medicine and rehabilitation by conducting a scoping review (ScR) and identifying any literature gaps.

**METHODS**

**Study design**

We followed a six-stage methodological framework developed and suggested by Arksey and O’Malley. The reporting was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Scoping Review (PRISMA-ScR) guidelines and conducted following the extensions to the original framework recommended by the Joanna Briggs Institute methodology for ScR. PRISMA-ScR reporting checklist was provided in online supplemental file 1A. The protocol was prospectively stored in OSF (https://osf.io/6vx5a/).

**Identifying the research question**

This ScR aimed to identify the existing evidence about the safety of physical agents applied by healthcare professionals. The specific aims were:

- To map the landscape of evidence about the safety of physical agents.
- To summarise the safety classifying AEs reported according to their severity.
- To identify and analyse knowledge gaps for each physical agent, considering the reporting of the certainty of the evidence and the type of analyses presented by SRs (eg, qualitative and quantitative syntheses).

**Inclusion criteria**

**Population**

We considered adults experiencing common physical medicine and rehabilitation disorders (eg, musculoskeletal, multiple chronic conditions). We excluded studies focusing on specific conditions (eg, cancer pain, dysphagia, life-threatening conditions, wounds, ulcers, labour pain) or those unrelated to healthcare (eg, cosmetology, aesthetics).

**Concept**

We included studies that explored and reported safety regarding AEs related to applying physical agents. We considered physical agents used in physical medicine and rehabilitation such as cryotherapy, electrical stimulation (any type), transcutaneous electrical nerve stimulation (TENS), extracorporeal shock wave therapy (ESWT), diathermy (eg, SWD, microwave), laser therapy (eg, LLLT) and ultrasound. Physical agents used as a vehicle for drug administration through the skin (eg, iontophoresis) or requiring the adoption of needles were excluded, as well as therapies without superficial application (eg, ultraviolet and radiant heat).

**Context**

Outpatient and inpatient physical medicine and rehabilitation settings managed by healthcare professionals.

**Type of evidence sources**

We primarily searched for SRs, including any study designs (eg, both randomised controlled trials (RCTs) and non-randomised intervention studies (NRISs)) assessing physical agents compared with any control group, except for head-to-head study designs (eg, TENS vs electrical stimulation, low-dose vs high-dose ESWT).

**Search strategy**

We searched MEDLINE (via PubMed), Cochrane Library, EMBASE and PEDro using a three-step approach to select English SRs published from January 2011 to 29 September 2021. All details are reported in online supplemental file 1B. The complete electronic search strategies for each database are reported in online supplemental file 1C.

**Study selection**

Two authors (SB, LP) independently tested the eligibility criteria by piloting a random sample of 25 articles and started screening when 75% agreement was achieved. EndNote (The EndNote Team, V.20; Clarivate, Philadelphia, Pennsylvania, USA; www.endnote.com) and Rayyan (Qatar Computing Research Institute, Qatar; www.rayyan.ai) software were used to manage this phase. Then, they independently assessed the full text of relevant studies for inclusion. Finally, disagreements were solved through discussion with a third author (SG).

**Charting the data**

Two authors (SB, LP) independently extracted the following data from the included SRs: name of the first author, publication year, the SR population, intervention, comparison and outcome question; number and type of study design of included studies; AE findings (in terms of quantitative/qualitative synthesis); measures of effects (eg, risk ratio (RR), OR, risk difference) with its 95% CIs and certainty of the evidence. In case of missing information (eg, missing comparisons, missing description of ESWT type), they consulted primary studies included in the SRs.

**Collating, summarising and reporting the results**

The review results were presented narratively following the PRISMA-ScR reporting guidance. First, the available evidence was summarised according to the SR qualitative...
and quantitative syntheses and reported by comparisons (eg, TENS vs placebo). Then, when the type of AE was reported, the severity was summarised according to the Common Terminology Criteria: grade 1 corresponds to mild AE (eg, mild pain, skin reddening); grade 2 to moderate AE (eg, infection); grade 3 to severe AE (eg, pneumonia); grade 4 to life-threatening or disabling AE; and grade 5 to death related to AE.\(^{18}\) In the case of studies not reporting the type of AE that occurred but only the severity (eg, not serious), we transparently reported it. Finally, the reporting of the certainty of the evidence was mapped.

**Consultation with stakeholders**

The Italian Association of Physiotherapy (AIFI), a scientific body of Italian physiotherapists, was consulted. In addition, AIFI content experts (AIFI Consortium) on physical agents, pelvic floor, musculoskeletal disorders and sports medicine provided additional insights about potential studies to include in this review.

**Patient and public involvement**

No patient was involved.

### RESULTS

After the duplicate removal, 3233 records were identified. Finally, 117 SRs were included (references are reported in online supplemental file 2) (figure 1).

**General characteristics of the SR**

The total number of primary studies included in the SRs evaluating physical agents was 1233. The median year of publication was 2017 (IQR=2014–2020), while the median year of the literature search performed by the SRs was 2016 (IQR=2014–2019). Most of the SRs included RCTs (77%). The most studied physical agents were ESWT (15%), TENS (13%) and electrical stimulation (12%). The most studied population presented musculoskeletal disorders (67%) (table 1).

Online supplemental table 1 presents the general characteristics of each SR.

**Objective 1: available evidence on safety**

Overall, 91 out of 117 SRs reported available evidence on safety. The remaining 22 SRs planned the outcome, but the primary studies did not report it, and four SRs reported the outcome only in the abstract or conclusion with no data in the results.

Overall, 23 SRs, including 105 RCTs, provided a quantitative synthesis of the occurrence of AEs (19.7%). No differences in experiencing AEs were found in all physical agents except for ESWT, which showed a statistically significant associated risk of experiencing mild AEs (eg, pain, erythema, haematoma) compared with the control group in three SRs out of five. One SR reported an increased associated risk of AEs in focal ESWT compared with placebo, with low certainty of evidence (RR=3.61; 95% CI=2 to 6.52).\(^{18}\) The remaining two SRs reported increased AE risks in the ESWT group, with ORs ranging from 3.06 (95% CI from 1.18 to 7.93)\(^{19}\) (including both radial and focal) to 14.05 (95% CI from 1.76 to 112.20)\(^{20}\) (focal ESWT) compared with placebo and corticosteroid injections, respectively. All details are reported in online supplemental table 2.

**Objective 2: classification of AEs according to the severity and interventions**

Overall, 34.7% reported no AEs, 25.4% no serious, 30.9% mild, 4.4% moderate and 0.9% severe, and 3.7 unclear types of AEs (table 2). Online supplemental table 3 shows the available evidence provided by qualitative and quantitative syntheses stratified by the AE severity.
<table>
<thead>
<tr>
<th>Physical agents</th>
<th>Cardiorespiratory</th>
<th>Musculoskeletal</th>
<th>Neurological</th>
<th>Oncology</th>
<th>Pelvic floor</th>
<th>Study design</th>
<th>Search year</th>
<th>Overall</th>
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</thead>
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<tr>
<td>Cryotherapy</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>RCT-mixed</td>
<td>2012 (2011–2013)</td>
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<td>Electrical stimulation</td>
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<td>2</td>
<td>4</td>
<td>0</td>
<td>7</td>
<td>2017 (2016–2018)</td>
<td>14 (12.0)</td>
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<tr>
<td>TENS</td>
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<td>10</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>2016 (2014–2017)</td>
<td>15 (12.8)</td>
<td></td>
</tr>
<tr>
<td>FES</td>
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<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2019 (2019–2019)</td>
<td>6 (5.1)</td>
<td></td>
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<td>ESWT</td>
<td>0</td>
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<td>2</td>
<td>0</td>
<td>1</td>
<td>2018 (2015–2019)</td>
<td>17 (14.5)</td>
<td></td>
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<tr>
<td>Laser therapy</td>
<td>0</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2018 (2018–2019)</td>
<td>11 (9.4)</td>
<td></td>
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<td>Magnetotherapy</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>2014</td>
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<td>PEMF</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2018</td>
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<td>Diathermy (microwave, SWD)</td>
<td>0</td>
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<td>2014 (2011–2016)</td>
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<td>Ultrasound</td>
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<td>0</td>
<td>0</td>
<td>2017 (2013–2020)</td>
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<td>More than one physical agent*</td>
<td>0</td>
<td>22</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>2015 (2012–2017)</td>
<td>31 (26.5)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2</td>
<td>78</td>
<td>22</td>
<td>2</td>
<td>13</td>
<td>2016 (2014–2019)</td>
<td>117 (100.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Example: heat, magnetotherapy or electrotherapy.

ESWT, extracorporeal shock wave therapy; FES, functional electrical stimulation; No, number; NRIS, non-randomised intervention study; PEMF, pulsed electromagnetic field; RCT, randomised controlled trial; SRs, systematic reviews; SWD, short-wave diathermy; TENS, transcutaneous electrical nerve stimulation.
CRYOTHERAPY
Overall, one SR reported AEs in five RCTs (online supplemental table 4) versus no treatment. No AE was reported.

ELECTRICAL STIMULATION
Overall, 13 SRs reported AEs in 50 RCTs and 12 NRISs (online supplemental tables 5 and 6).

Eight SRs evaluated electrical stimulation versus conservative treatment (11 RCTs). No AE was reported in eight RCTs, mild in two RCTs and moderate in one RCT (for both groups).

Two SRs evaluated electrical stimulation versus pharmacological treatment (five RCTs). No AE was reported.

Eight SRs evaluated electrical stimulation versus inert treatment (24 RCTs). No AE was reported in nine RCTs, mild in two, moderate in two (one study also reported AEs in the control group) and not serious in four. There was no statistically significant difference between the two groups in the remaining four. One RCT reported AEs related to treatment without specifying them. Two RCTs reported severe AEs in both groups.

Three SRs evaluated electrical stimulation versus no treatment (three RCTs). No AEs were reported.

One SR evaluated electrical stimulation versus more than one treatment (seven RCTs). AEs were reported in 31 cases out of 728 participants.

Four SRs evaluated electrical stimulation in studies without a control group (12 NRISs). No AEs were reported in six NRISs, mild in one, moderate in one (two tetraplegic patients) and not serious in four.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION
Overall, 15 SRs reported AEs in 49 studies (42 RCTs, 7 NRISs) (online supplemental table 6).

Seven SRs evaluated TENS versus conservative treatment in 11 RCTs. No AEs were reported in 10 studies (9 RCTs, 1 quasi-RCT) and mild AE in 1 RCT.

Three SRs evaluated TENS versus pharmacological treatment in three RCTs. No AE was reported in one RCT, while mild AE was in two RCTs.

Eight SRs evaluated TENS versus inert treatment in 17 RCTs. No AE was reported in nine RCTs, while mild AE was in eight RCTs.

One SR evaluated TENS versus more than one treatment in one RCT. No AE was reported.

Two SRs evaluated TENS versus no treatment in three RCTs. No AE was reported in two RCTs, while mild AEs were reported in one RCT.

Two SRs evaluated TENS in studies without a control group in six NRISs. No AE was reported.

One SR evaluated TENS versus different treatments in one RCT. Mild AEs were reported.

FUNCTIONAL ELECTRICAL STIMULATION
Overall, five SRs reported AEs in 6 RCTs, 3 NRISs and 43 RCTs+NRISs (online supplemental table 7).
Four SRs evaluated functional electrical stimulation (FES) versus other comparisons (more than one treatment/undefined treatment) in 6 RCTs, 8 NRISs and 35 RCTs+NRISs. No AE was reported in 6 RCTs, not serious in 35 RCT+NRISs and moderate in 8 NRISs.

Two SRs (three NRISs) evaluated FES in studies without a control group. No AE was reported.

**EXTRACORPOREAL SHOCK WAVE THERAPY**

Overall, 19 SRs reported AEs in 87 RCTs, 3 NRISs and 106 RCTs+NRISs (online supplemental table 8).

Seven SRs evaluated ESWT versus conservative treatment (11 RCTs). No AE was reported in five RCTs, mild in five and not serious AEs in one.

Two SRs evaluated ESWT versus pharmacological treatment (seven RCTs). No AE was reported in one RCT, mild in three RCTs and not serious in three RCTs.

Ten SRs evaluated ESWT versus inert treatment (31 RCTs). No AE was reported in 7 RCTs, mild in 20 RCTs and not serious in 3 RCTs. One study had one unclear AE in the experimental group and three unclear in the control group.

Three SRs evaluated ESWT versus no treatment (four RCTs). No AE was reported in one RCT, mild in two RCTs and moderate in one RCT.

Five SRs evaluated ESWT versus more than one treatment/undefined treatment (22 RCTs, 106 RCTs+NRISs). No AE was reported in one RCT, mild in six, moderate in one (in both groups) and not serious AEs in one SR of 106 RCTs/NRISs and one SR of 14 RCTs.

Three SRs evaluated ESWT versus regenerative treatment (nine RCTs). No AE was reported in six and mild in two. One study reported that some patients experienced mild side effects in the treatment area, which were not specified.

One SR evaluated ESWT versus alternative treatment (three RCTs). No AE was reported.

Two SR (three NRISs) evaluated ESWT in studies without a control group. No AE was reported in two NRISs and mild in one.

The distinctions between AEs in radial and focal ESWT are reported in online supplemental table 8A,B.

**LASER THERAPY**

Overall, 15 SRs reported AEs in 134 studies (87 RCTs, 47 NRISs) (online supplemental table 9).

Seven SRs evaluated laser therapy versus conservative treatment (19 RCTs, 2 NRISs). No AE was reported.

Thirteen SRs evaluated laser therapy versus inert treatment (50 RCTs, 1 NRIS). No AE was reported in 44 studies (43 RCTs, 1 NRIS), mild in 6 RCTs and moderate in 1 RCT.

One SR evaluated laser therapy versus no treatment (one RCT). No AE was reported.

Two SRs evaluated laser therapy in studies without a control group (2 RCTs, 53 NRISs). In one cohort study, there were mild AEs reported in 44 studies (1 RCT, 43 NRISs), moderate AEs in 10 cohort studies and severe AEs but not related to treatment (arm infection in one participant).

**DIATHERMY (MICROWAVE AND SWD)**

Overall, six SRs reported AEs in 14 RCTs (online supplemental table 12).

Three SRs evaluated diathermy versus conservative treatment (four RCTs). No AE was reported in three RCTs and mild in one RCT.

Two SRs evaluated diathermy versus pharmacological treatment (two RCTs). No AEs were reported in one RCT, while no differences in AEs between the two treatment groups were reported in the other RCTs.

One SR evaluated diathermy versus inert treatment (seven RCTs). No AEs were reported in six RCTs and two mild AEs in one RCT (in both experimental and control groups).

One SR evaluated diathermy versus no treatment (one RCT). Ten mild AEs (four patients) were reported in one RCT.

**HOT THERMAL AGENTS**

Overall, two SRs reported AEs in four RCTs (online supplemental table 13).

Two SRs evaluated hot thermal agents versus conservative treatment in two RCTs. No AE was reported.

One SR evaluated hot thermal agents versus pharmacological treatment (two RCTs). No serious AE was reported.

One SR evaluated hot thermal agents versus inert treatment (one RCT). No serious AE was reported.

**MAGNETOTHERAPY**

Overall, one SR reported AEs in three RCTs (online supplemental table 10).

Two SRs evaluated magnetotherapy versus inert treatment (three RCTs). No AE was reported.

**PULSED MAGNETIC FIELDS**

Overall, three SRs reported AEs in eight studies (seven RCTs, one NRIS) (online supplemental table 11).

One SR evaluated pulsed magnetic fields versus conservative treatment (one RCT). No AE was reported.

Two SRs evaluated pulsed magnetic fields versus inert treatment (six RCTs). No AE was reported in four RCTs, while mild AEs were reported in two RCTs.

One SR evaluated pulsed magnetic fields versus no treatment (one NRIS). Mild AEs were reported in the experimental group, whereas moderate AEs were reported in the control group (median nerve compression).

**ULTRASOUND**

Overall, 15 SRs reported AEs in 51 RCTs (online supplemental table 14).
Six SRs evaluated ultrasound versus conservative treatment in 12 RCTs. No AE was reported in 11 RCTs, while 1 RCT did not clearly report which AEs had occurred.

Two SRs evaluated ultrasound versus pharmacological treatment in two RCTs. No AE was reported in one RCT, while drug-related AEs were reported in the second RCT.

Twelve SRs evaluated ultrasound versus inert treatment in 37 RCTs. No AE was reported in 28 RCTs, mild AEs were reported in 5 RCTs and severe AEs (pulmonary embolus) were reported in 3 RCTs. One RCT did not clearly report which AEs had occurred.

**MORE THAN ONE PHYSICAL AGENT**
Overall, four SRs reported AEs in 23 RCTs. All details are reported in online supplemental table 15.

**Objective 3: knowledge gaps considering the reporting of the certainty of evidence and the type of analyses presented by SRs (eg, qualitative and quantitative syntheses)**
Overall, 21 (17.9%) SRs out of 117 assessed the certainty of evidence on AE outcome. Of these, 12 SRs (52.2%) provided quantitative synthesis and 11 SRs (14.3%) provided qualitative synthesis (two SRs provided both types of synthesis) (online supplemental table 16).

**DISCUSSION**
This ScR aimed to map the landscape of evidence about safety outcomes in 117 SRs assessing physical agents with skin-applied components. The most studied physical agents were ESWT (15%), TENS (13%) and electrical stimulation (12%). In addition, the most studied population was patients with musculoskeletal disorders (67%). Overall, one-fifth of SRs reported a quantitative synthesis on the occurrence of AEs. Moreover, 18% of SRs assessed the certainty of the evidence on safety outcomes, with half assessments reported in SRs with the quantitative synthesis.

At the current status of the literature, physical agents appear to be safe, as around one-third of the primary studies included by SRs reported no AEs. In contrast, severe AEs occurred in less than 1% of the sample, reported in the control group or were not directly related to the physical agents (eg, pneumonia).

Among all physical agent interventions, ESWT showed a statistically significant increased risk of having AEs compared with control in three out of five SRs reporting the quantitative synthesis, with only one providing low certainty of evidence (imprecision of the effects for a small sample size (<200 events)) meaning that the true effect might be markedly different from the estimated effect. Moreover, it should be taken into account that some CIs can be overestimated when meta-analyses do not use appropriate statistical approaches for a low number of events (ie, Peto odds). Then, the occurrence of AEs in both radial and focal ESWT when compared with pharmacological or inert treatment was expected, known and solicited (eg, pain and erythema). Analogously, in SRs not providing quantitative synthesis, most related AEs (65%) in ESWT were mild/not serious (such as temporary pain, bruising, local swelling, erythema, discomfort) and were similar when using radial or focal modalities. The ESWT treatment itself is unpleasant or painful as a side effect but not as a complication. Indeed, no severe complications are expected if ESWTs are performed as recommended.

**RESEARCH GAPS AND IMPLICATIONS**
The poor planning, assessment and standardisation in collecting AEs in primary studies can affect the evidence. We found a low rate of AEs in the literature (around 1% of severe AEs); however, these data can be underestimated considering the real-world data relating to patient health status (eg, associations, electronic health records).

Sparse initiatives across countries are present such as the US Food and Drug Administration (FDA) repository that reports AEs related to FDA-approved devices and the US Healthcare Providers Service Organization that publishes information about claims related to physical agents. Analogously, the European Commission has introduced the European database on medical devices to access information for the public and healthcare professionals. However, the collection of AEs in non-pharmacological interventions can differ from pharmacological interventions, where regulatory agencies have established procedures for assessment, monitoring and reporting.

In non-pharmacological interventions, the heterogeneous AE taxonomy and divergent methods of seeking, reporting, verifying and classifying AEs can impact the effect estimates. Therefore, AEs should be present in the core outcome set of any medical condition irrespective of the type of intervention. Furthermore, the assessment, monitoring and reporting should be mandatory in protocols of primary studies and the prospective registration and public access to study data fulfilling ethical obligations towards patients and ensuring a basis for fully informed decision-making in the healthcare system.

The improvement in the AE reporting can increase the quantitative data in SRs with a better assessment of the certainty of evidence. Therefore, approaches such as the Grading of Recommendations Assessment, Development, and Evaluation should be recommended. An extension of the Consolidated Standards of Reporting Trials statement has been developed to provide detailed recommendations on reporting harms in primary studies of non-pharmacological interventions. However, the findings of this ScR revealed that AEs were under-reported in the included studies, affecting the validity of the underlying literature.

**STRENGTH AND LIMITATIONS**
This ScR is the first study mapping the landscape of evidence about the safety of a broader range of physical
agents than a previous study.\(^1\) We provided a deep analysis stratifying each comparison assessed in primary studies and categorising AEs according to their severity. In addition, we followed the established standards of reporting and conduct to increase the external validity.\(^1\)\(^3\)\(^4\)

This study presents some limitations. First, we pragmatically decided to include some common physical agents incorporating heterogeneity of different use and definitions across countries. Second, we limited SRs published in the last 10 years, not considering seven non-English SRs.

Indeed, the type of AEs or the number of events/patients experiencing AEs in experimental and control groups was not always present in SRs, as well as descriptions of interventions (eg, radial or focal ESWT) and other parameters (eg, alternating vs direct current, voltage, amperage, frequency, current density). Indeed, for detailed information of interventions, we had to go through the related primary studies. In addition, primary studies did not systematically assess the outcome (22 SRs out of 117 planned but did not report AEs), or the outcome was reported in only half of the included studies. Consequently, we could not classify the severity of all AEs reported. This can be due to the inclusion of NRIS in 23% of SRs. Because of no mandatory registration for NRIS as for RCTs, most NRISs are not registered, and the outcome can be poorly reported.\(^3\)\(^3\) Fourth, we did not search grey and unpublished literature.\(^3\)\(^4\) Finally, we cannot ensure the validity of the included SRs since we did not assess their methodological quality through AMSTAR II\(^3\)\(^5\) as we cannot ensure validity of the methods used for meta-analyses because the aim of the SR is limited to mapping relevant evidence.\(^1\)\(^4\)

**CONCLUSION**

Current evidence from SRs investigated the safety of most physical agents used in physical medicine and rehabilitation. No significant harm from these interventions was found except for ESWT, which increased the risk of experiencing mild (known) AEs. Improving the reporting of AEs and their classification should be of priority in primary studies to be pooled in meta-analysis and to fully assess the certainty of evidence.

**REFERENCES**