

## SYSTEMATIC REVIEW &amp; META-ANALYSIS

## Effectiveness of clown therapy on procedural pain in children with cerebral palsy. A meta-analysis

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### Findings:

*Although the results of the included studies seem promising, substantial heterogeneity and the risk of bias indicate the need for more rigorous studies in this direction.*

### ABSTRACT

**BACKGROUND:** Nearly 10% of the pain that affects children with cerebral palsy (CP) results from a medical procedure. Clown therapy is a popular distraction technique to reduce pain; some systematic reviews evaluate the efficacy of this intervention in the pediatric setting, but none on children with CP.

**AIM:** To evaluate the effectiveness of clown therapy on procedural pain in children with CP.

**METHODS:** Systematic review with meta-analysis of clinical trials with control group. Retrieval of studies by querying biomedical databases, online resources and trial registers. Clown therapy was compared with standard care. The primary outcome was the pain level after surgery. The risk of bias was assessed with RoB 2. Effect size was calculated with a random effects model.

**RESULTS:** Three studies with 164 patients were included. The risk of bias is high for two studies and raises some concerns for one. All studies analyzed the effect of clown therapy on procedural pain after botulinum toxin injection. There was a statistically non significant reduction in pain in the intervention group compared to the control group (SMD: -0.20, 95% CI: -0.56, 0.17). The heterogeneity between studies is high.

**CONCLUSION:** Clown therapy for procedural pain from botulinum toxin injections in children with CP seems effective but the methodological limitations of the studies do not allow a definitive judgment. There is a lack of studies evaluating the effect of the intervention on other procedures that children with CP undergo periodically.

**KEYWORDS:** *Clown Therapy, Procedural Pain, Children, Cerebral Palsy*

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REVISIONE SISTEMATICA &amp; META-ANALISI

## La Clown terapia per il dolore procedurale nei bambini con paralisi cerebrale. Revisione sistematica e Meta-analisi

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### Riscontri:

*Nonostante i risultati degli studi inclusi siano promettenti, una forte eterogeneità ed il rischio di bias indicano la necessità di studi più rigorosi in questa direzione.*

### ABSTRACT

**BACKGROUND:** Quasi il 10% del dolore che colpisce i bambini con paralisi cerebrale (PC) deriva da una procedura medica. La clown terapia è una diffusa tecnica di distrazione per ridurre il dolore; alcune revisioni sistematiche valutano l'efficacia di questo intervento in ambito pediatrico, ma nessuna su bambini con PC.

**OBIETTIVO:** Valutare l'effetto della clown terapia sul dolore procedurale nei bambini con PC.

**METODI:** Revisione sistematica con meta-analisi di trial clinici con gruppo di controllo. Reperimento degli studi tramite interrogazione di database biomedici, risorse online e registri di trial. La clown terapia è stata confrontata con le cure standard. L'esito primario era il livello di dolore dopo l'intervento. Il rischio di bias è stato valutato con RoB 2. La dimensione d'effetto è stata calcolata con un modello a effetti casuali.

**RISULTATI:** Tre studi con 164 pazienti sono stati inclusi. Il rischio di bias è alto per due studi e solleva qualche dubbio per uno. Tutti gli studi hanno analizzato l'effetto della clown terapia sul dolore procedurale dopo l'iniezione di tossina botulinica. È stata rilevata una riduzione statisticamente non significativa del dolore nel gruppo di intervento rispetto a quello di controllo (DSM: -0,20, IC 95%: -0,56, 0,17). L'eterogeneità tra gli studi è elevata.

**CONCLUSIONE:** La clown terapia per il dolore procedurale da iniezioni di tossina botulinica nei bambini con PC sembra efficace ma i limiti metodologici degli studi non consentono un giudizio definitivo. Mancano studi che valutino l'effetto dell'intervento su altre procedure a cui si sottopongono periodicamente i bambini con PC.

**KEYWORDS:** *Clown Terapia, Dolore Procedurale, Bambini, Paralisi Cerebrale*

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## BACKGROUND

Cerebral palsy (CP) includes a group of neurological disorders that affect an individual's movement, posture, and balance [1]. In about nine out of ten cases, the etiology can be traced back to the perinatal period [2]; it is the most frequent cause of childhood physical disability and affects about 2-3 children per 1000 live births [3-8]. CP results in movement disorders (spasticity, dystonia) [9, 10] and includes chronic pain, cognitive disorders [11, 12], deficits in speech and vision [13], behavioral problems, and seizures [14, 15]. Pain affects 67-84% of individuals [11, 16-18]; despite multiple causes [12, 13, 19], it generally results from spastic muscle contractions [20, 21]. Procedures that children with CP undergo periodically to improve motor performance and reduce pain can exacerbate the symptom and increase discomfort [17, 22, 23, 24, 25]: nearly 10% of the pain they experience results from procedures [26]. Even in children with CP, diagnostic or therapeutic procedures may cause pain, anxiety, or fear [27] but in addition they have greater need for repeated treatment over time and, if with intellectual disability, have difficulty communicating pain [28]. Quality health care must be able to address and manage procedural pain [29] in order to produce a positive effect on anticipatory anxiety [30]. Short- and long-term psychological consequences and unsatisfactory adherence to care may occur in cases of suboptimal symptom management [31, 32]. Children's acute pain should first be addressed by resorting to nonpharmacological interventions such as distraction techniques [33]. These include clown therapy, implemented by people who have undergone specific training (clown doctors) who through a clown suit establish a relationship with children who are hospitalized. Through play and fun, clown doctors

help young patients meet their need for interaction and support their emotional expression; they also enhance coping skills for optimal management of procedural pain, anxiety and fear [34]. The efficacy of the intervention finds its physiological rationale from the experimental observation that fun and laughter stimulate the production of beta-endorphins, which have strong analgesic and excitatory properties and an anesthetizing effect similar to morphine and opioid substances [35]. Clown therapy in pediatric settings is an increasingly popular intervention; attention to this distraction technique is evidenced by the presence of several systematic reviews evaluating its effectiveness [36-41]. However, there are no known reviews focused on the effect of the intervention for procedural pain in children with CP.

## AIM

To test the effectiveness of clown therapy on procedural pain in children with CP.

## METHODS

### Inclusion criteria

Randomized, quasi-randomized, or non randomized clinical trials with control group on the effect of clown therapy for procedural pain of children with CP were included. Inclusion criteria were (1) participants: pediatric subjects with CP undergoing medical procedures; (2) intervention: clown therapy clown doctors; (3) control: standard of care (parent support  $\pm$  other distraction techniques  $\pm$  analgesia or sedation); (4) outcome: (a) primary: procedural pain; (b) secondary: child and/or parent anxiety; (5) care setting: any.

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## Search strategy

The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42022325956). The search for papers of interest was performed until June 2, 2022 on the biomedical databases Cochrane Library, MEDLINE, CINAHL, EMBASE, PsycINFO, Web of Science, Scopus. The keywords used were "cerebral palsy" associated with pain and "medical clown," "clown therapy," clowning, clown, "clown doctor," and "hospital clown" (Table 1). No language or publication date limits were applied.

The search was also extended to these online resources: LILACS, sciELO, CNKI, BASE, TRIP Medical Database.

To retrieve other recently completed studies, the following registries were consulted: International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, International Standard Randomised Controlled Trial Number (ISRCTN) registry, EU Clinical Trials Register Bibliographies of relevant reviews and eligible studies were searched. The corresponding authors of the latter were contacted by e-mail to find out if they knew of other studies of interest not intercepted by our search. Finally, the leading journals in the field and those that published the eligible studies were consulted.

Cochrane Library	MEDLINE	EMBASE	CINAHL	PsycINFO	Web of Science	Scopus
#1 ("cerebral palsy")	#1 "cerebral palsy"	#1 'cerebral palsy'	#1 "cerebral palsy"	#1 "cerebral palsy".mp	#1 "cerebral palsy" (All Fields)	#1 TITLE-ABS-KEY ("cerebral palsy")
#2 (pain)	#2 pain	#2 pain	#2 pain	#2 pain.mp	#2 pain (All Fields)	#2 TITLE-ABS-KEY (pain)
#3 (clown)	#3 clown	#3 clown	#3 clown	#3 clown.mp	#3 clown (All Fields)	#3 TITLE-ABS-KEY (clown)
#4 (clowning)	#4 clowning	#4 clowning	#4 clowning	#4 clowning.mp	#4 clowning (All Fields)	#4 TITLE-ABS-KEY (clowning)
#5 (clowntherapy)	#5 clowntherapy	#5 clowntherapy	#5 clowntherapy	#5 clowntherapy.mp	#5 clowntherapy (All Fields)	#5 TITLE-ABS-KEY (clowntherapy)
#6 ("clown therapy")	#6 "clown therapy"	#6 'clown therapy'	#6 "clown therapy"	#6 "clown therapy".mp	#6 "clown therapy" (All Fields)	#6 TITLE-ABS-KEY ("clown therapy")
#7 ("medical clown")	#7 "medical clown"	#7 'medical clown'	#7 "medical clown"	#7 "medical clown".mp	#7 "medical clown" (All Fields)	#7 TITLE-ABS-KEY ("medical clown")
#8 ("hospital clown")	#8 "hospital clown"	#8 'hospital clown'	#8 "hospital clown"	#8 "hospital clown".mp	#8 "hospital clown" (All Fields)	#8 TITLE-ABS-KEY ("hospital clown")
#9 ("clown doctor")	#9 "clown doctor"	#9 'clown doctor'	#9 "clown doctor"	#9 "clown doctor".mp	#9 "clown doctor" (All Fields)	#9 TITLE-ABS-KEY ("clown doctor")
#10 #3 OR #4 OR #5 OR #6 OR # 7OR # 8 OR #9	#10 #3 OR #4 OR #5 OR #6 OR # 7OR # 8 OR #9	#10 #3 OR #4 OR #5 OR #6 OR # 7OR # 8 OR #9	#10 #3 OR #4 OR #5 OR #6 OR # 7OR # 8 OR #9	#10 #3 OR #4 OR #5 OR #6 OR # 7OR # 8 OR #9	#10 #3 OR #4 OR #5 OR #6 OR # 7OR # 8 OR #9	#10 #3 OR #4 OR #5 OR #6 OR # 7OR # 8 OR #9
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Table 1: Search strategy.

## Study selection and data extraction

Independently, the authors performed querying of biomedical databases and online resources, screening of records by title and abstract, and in controversial cases also of full-text. Any disagreements were resolved through comparison and discussion. From each eligible study, through a

standardized template, the authors independently extracted the following data and information: first author and year, study design, country, setting, procedure, participants, exclusion criteria, intervention, control, primary outcome and evaluation method, results, any additional notes.

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## Risk of bias

Independently, the risk of bias was assessed with the Risk of Bias 2 (RoB 2) tool [42]. Graphical restitution was performed with the Risk-of-bias VISualization (robvis) tool [43].

## Data analysis and synthesis

The extracted data were analyzed with ProMeta© Version 3.0 software. Overall effect size calculation was performed with a random effects model and the creation of forest plots in the case of at least two studies for each outcome. Standardized mean difference (SMD) was calculated for continuous measures. The resulting overall effect was considered small, moderate or large according to Cohen's *d* thresholds of 0.2, 0.5 and 0.8 [44]. The 95% confidence interval was considered to represent the deviation from the point estimate for each individual study and from the global estimated value for the aggregated studies. The presence of heterogeneity ( $p < 0.05$ ) among studies was assessed with the Cochran Q test [45] and the degree of heterogeneity was quantified with the Higgins I<sup>2</sup> index [46]. Values of I<sup>2</sup>  $\leq 30\%$ , 30-60%, 60-90% or  $> 90\%$  were assigned a low, moderate, high or very high level of heterogeneity [47].

## Sensitivity analysis

In case of at least one outlier study, a sensitivity analysis was performed by regenerating a meta-analysis after its exclusion.

## Additional analyses

If possible, analyses were planned to assess the effectiveness of the intervention according to gender, age, severity of cerebral palsy, and level of intellectual disability of participants.

## Publication bias

Inspection of the funnel plot [48] and application of the Trim and Fill method [49] on it in the case of a meta-analysis with at least five studies was planned in order to check for publication bias risk. Objective assessment of publication bias was carried out using Egger's test [50] and Begg and Mazumdar's test [51]. The study was conducted and presented in accordance with PRISMA guidelines [52].

## Summary of results

Overall assessment of the quality/certainty of evidence was independently performed using the GRADE approach [53] applied to the results of the meta-analysis. Disagreements that arose were resolved by comparison and discussion.

## RESULTS

### Selection of studies

The electronic database search returned 50 records. Figure 1 shows the selection process. Bibliographies of eligible studies and journal searches yielded no other relevant studies. The corresponding authors of the included studies were contacted by e-mail; none were aware of additional studies of interest.

Ultimately, three studies met the inclusion criteria. A summary of their main characteristics is shown in Table 2.

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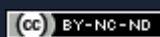
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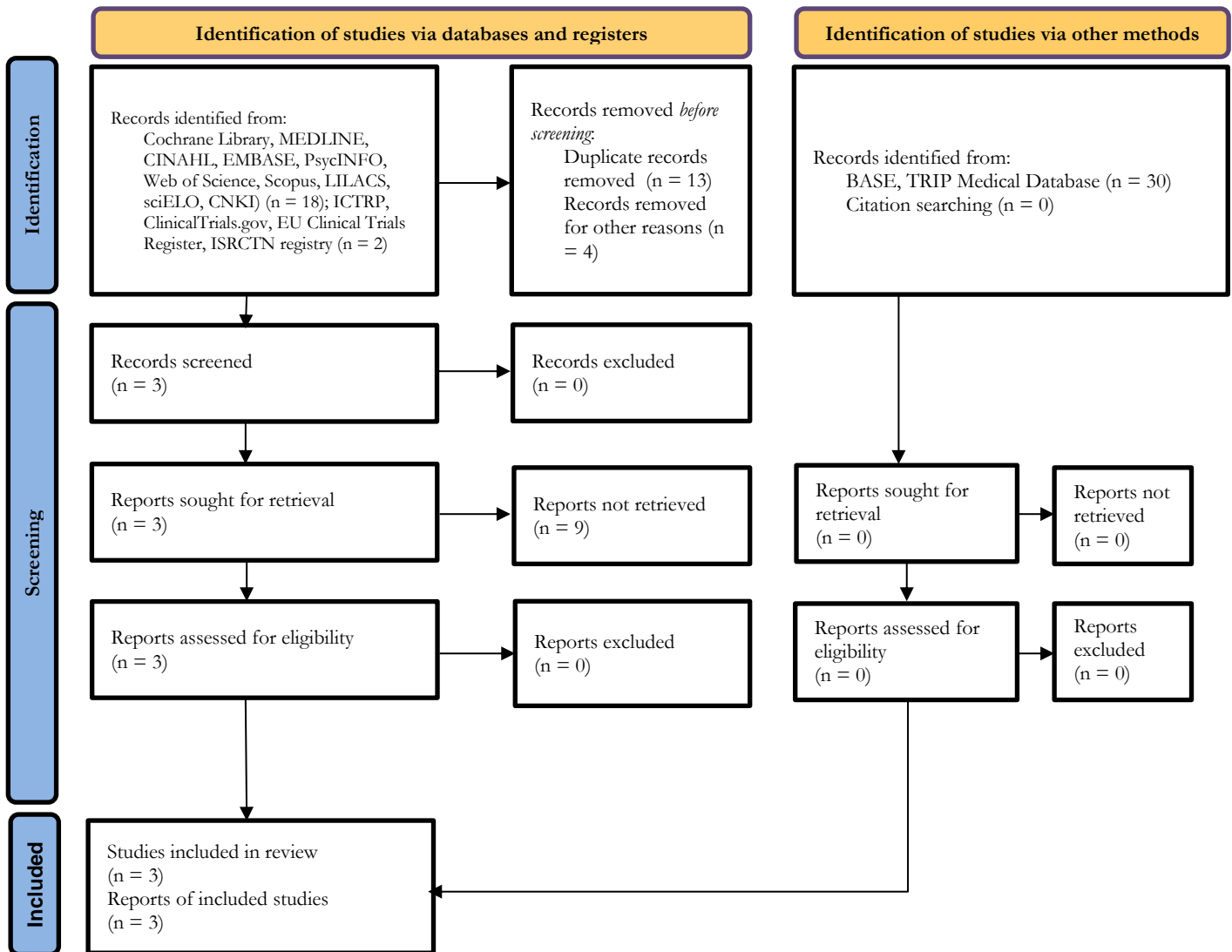
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Figure 1: Records screening.

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STUDY DESIGN, COUNTRY	SETTING	PROCEDURE	SAMPLE	EXCLUSION CRITERIA	INTERVENTION	CONTROL	PRIMARY OUTCOME AND EVALUATION METHOD	RESULTS	ADDITIONAL NOTES
Ben-Pazi, 2017 qRCT+cCT, Israel	Clinic	Botulinum toxin injection	45 children with an age range of 1.5 to 18 years Mean age 7.04 years 67% male Percentage of children at first injection: 100% All with cerebral palsy (mean GMFCS level: III)	Children with very limited communication skills, autism spectrum disorders, severe anxiety requiring general anesthesia	The children's parents are by their side throughout the procedure A gender not declared clown with certified experience and formal training course interacts with the child before, during, and after the procedure with distraction techniques based on the child's age, cognitive level, and personal preferences Following the procedure, the care staff interacts positively with the child and offers rewards in an effort to reshape negative memories toward a positive direction	The children's parents are by their side throughout the procedure Following the procedure, the treatment staff interacts positively with the child and offers rewards in an effort to reshape negative memories toward a positive direction	Assessment of procedural pain before and after sessions (VAS with 5-faces scale) Parents report personal perception of pain experienced by the child if the child is unable to report it (children younger than 5 years, children with significant intellectual disability)	Intervention group: n=20 VAS after procedure Mean value 2.89 Standard Deviation 1.36 Control group: n=25 VAS after procedure Mean Value 3.85 Standard Deviation 1.39 P value: 0.036	The procedure was performed under electromyographic guidance
Hansen, 2011 qRCT, Denmark	Clinic	Botulinum toxin injection	60 children with an age range of 1 to 15 years Mean age 4 years 57% male Percentage of children at first injection: 53% Most with cerebral palsy (mean GMFCS level: not stated)	Children with impaired sensitivity (e.g., subjects with spina bifida)	Children during the procedure are supported by their mother and sometimes their father as well The doctor, nurse, physical therapist and clown are also present The female clown interacts with the child 15 minutes before the procedure, during the procedure, and also several minutes after it is over The clown decides based on the child's emotional state the best ways to interact with the child	Parents and care team interact with the child before, during, and after the procedure	Assessment of procedural pain after the first botulinum toxin injection: duration of crying in seconds	Females Intervention group: 23 sessions Mean duration of crying: 62 seconds Control group: 25 sessions Mean duration of crying: 132 sec P value: 0.049  Males Intervention group: 30 sessions Mean duration of crying: 160 sec Control group: 43 sessions Mean duration of crying: 86 seconds P value: 0.139	86% of children received sedation with Midazolam
Houx, 2019 nRCT, France	Clinic	Botulinum toxin injection	59 children with an age range of 0 to 15 years Median age: 4 years 59% male Percentage of children at first injection: not stated 88% with cerebral palsy (GMFCS level I to III) 20% with moderate-to-severe cognitive disorders	Not stated	One to three male or female clowns may be present They use different strategies to interact and distract the child, depending on the child's age and the number of injections to be given The clown also supports the parents or caregivers and, at the end of the procedure, provides positive reinforcement to the child for future sessions	Children may listen to music, watch TV, play video games, or discuss topics of interest to them or suggested by the nurse or a caregiver Before the injection, the child or parent or caregiver is asked about particular interests or what would promote a relaxed atmosphere	Assessment of procedural pain after the session (FLACC scale with score 0-10)	Intervention group: 40 sessions FLACC after the procedure Median value: 1.5 Interquartile range: 0.5-3.4 Control group: 48 sessions FLACC after the procedure Median value: 2 Interquartile range: 1-3.2 P value: 0.349	The procedure was performed under electromyographic and/or ultrasonographic guidance An analgesic cream was applied to all children on the areas to be pricked at least 60 minutes before the procedure If there were no medical contraindications, N <sub>2</sub> O was administered 5 minutes before the procedure, and unless side effects occurred, administration continued throughout the procedure

cCT=crossover Clinical Trial; GMFCS = Gross Motor Function Classification System; nRCT=non Randomized Controlled Trial; qRCT=quasi Randomized Controlled Trial.

Table 2: Characteristics of the studies.

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### Characteristics of the studies

One study (55) consists of two separate studies: a quasi-randomized controlled clinical trial (qRCT) and a crossover study. One study is a qRCT (56), another is a non-randomised controlled clinical trial (nRCT) (57). A total of 164 children (61% male) with age range 0-18 years (mean age: 4-7 years), almost all with CP, were included. The sample size ranged from 45 (55) to 60 (56) individuals. Studies were conducted in Denmark (56), France (57) and Israel (55), all in hospital outpatient clinics. The common procedure was intramuscular injection of botulinum toxin (BTI); each session participants underwent could include one or more injections. In one study (55), children attended the session for the first time and were given clown therapy or standard of care; then, several months later, subjects were given another session and those who had received the intervention in the first session were given standard of care (and vice versa). When stated, children with severe limitations in communication skills (e.g., individuals with severe mental retardation) (55) or sensory impairments (e.g., individuals with spina bifida) were excluded from the trial (56). One study (55) did not report the use of sedatives or analgesics prior to the session, while in one study (56) most children (86%) had been given midazolam and in another had been given inhaled nitrous oxide (N<sub>2</sub> O) and analgesic cream had been applied to the areas where the injections were to be performed (57). In both cases preventive treatment was delivered to both the intervention and control groups. In addition, in the intervention group there was the presence of at least one clown doctor who interacted with the child before (55,56), during and after (55-57) the execution of the session in the presence of at least one parent/caregiver; the distraction techniques applied by the clown changed according to the age, cognitive

level, emotional state and preferences of the child as well as the duration of the session. In all studies the clown doctor was present on certain days of the week and at set times. In the control group, parents/caregivers and healthcare staff offered the child comfort, attention, and positive reinforcement (55,56), or even alternative distraction techniques (e.g., watching TV, listening to music, playing video games) (57). All studies assessed children's procedural pain, in one case also children's and parent's anxiety (57). The authors of one study (55) had the child assess pain with the 5-sided Visual Analogue Scale (VAS) immediately before and after the procedure; in the presence of children younger than 5 years or with significant intellectual disability it was the parents, using the same instrument, who assessed pain. In one study, pain assessment was performed by measuring the duration of crying in seconds after the first injection (56). The authors presented results separated by gender. In the most recent study (57), pain was measured during the session using the FLACC scale (58), with a second pain assessment made at the end of the session using a 100 mm VAS scale by children over 5 years old who were able to communicate and by parents. The level of anxiety was also measured with a 100 mm VAS scale before, during and 10 minutes after the session only by children over 5 years old who were able to communicate and their parents. The authors presented the results of the effect of the intervention on pain also as a function of some variables such as gender, age, presence or absence of cognitive impairment. Satisfaction with the intervention as perceived by the parent/caregiver and healthcare staff was investigated in two studies (55,56).

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## Risk of study bias

The risk of bias assessment of the included studies is summarized in Figure 2 and Figure 3. The studies raise some concerns about the randomization process and deviations from the intended interventions; the risk of bias due to lack of outcome data is low, as well as for that related to the selection of report outcomes. Two studies are at high risk of bias in outcome measurement [54, 56] and one is of

some concern [55]. Overall, the risk of bias is high for two studies [54, 56] and a source of some concern for one [55].

One study (55) stated for one of the authors a possible conflict of interest and that he had received partial financial support from a private foundation; the authors of another (56) stated that the clown's services had been paid for with donations from private organizations.

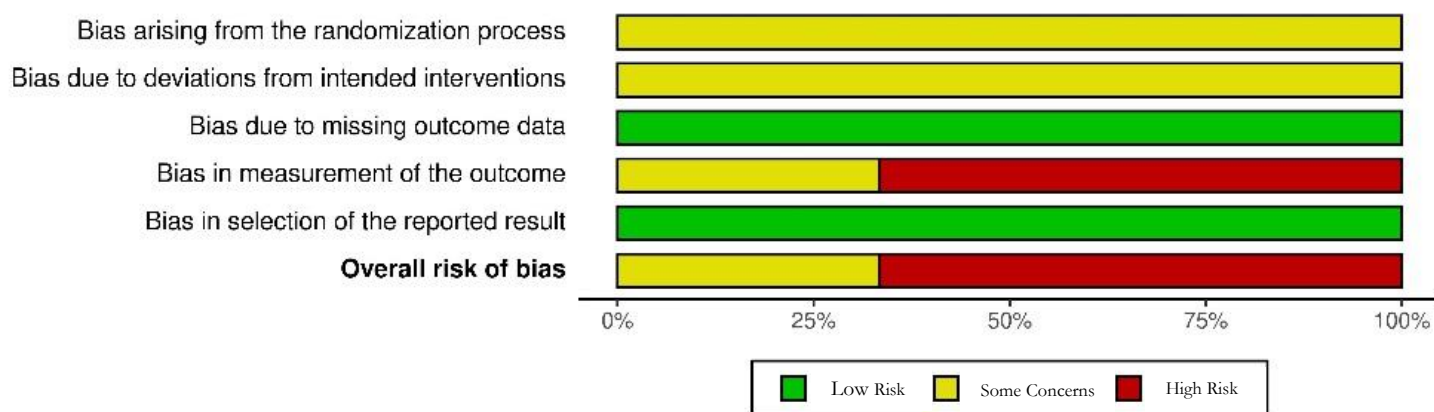


Figure 2: risk of bias assessment (part 1).

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Ben-Pazi 2017	-	-	+	X	+	X
Hansen 2011	-	-	+	-	+	-
Houx 2019	-	-	+	X	+	X

Domains:  
 D1: Bias arising from the randomization process.  
 D2: Bias due to deviations from intended intervention.  
 D3: Bias due to missing outcome data.  
 D4: Bias in measurement of the outcome.  
 D5: Bias in selection of the reported result.

Judgement  
 X High  
 - Some concerns  
 + Low

Figure 3: risk of bias assessment (part 2).

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## DATA ANALYSIS

### Procedural pain

The least recent study (56) presented results divided by participant sex and provided only the mean value. The most recent study (57) presented results using the median and interquartile range; with the application of a conversion technique the median was transformed to the mean (59,60) to allow comparison with other studies. Finally, the results of one study were presented with the mean and standard deviation (55). However, unlike the previous two studies, in this one the unit of analysis was the child and not the session. To use the session as the common unit of analysis and trace it back to the session, the supplementary file available online was analysed. Data useful for the meta-analysis and available across studies for the intervention and

control group were: number of sessions, mean value and exact p-value. Overall, the effect of clown therapy for procedural pain in children with CP was assessed for 332 sessions. The aggregate SMD is -0.20 (95% CI: -0.56, 0.17) in favor of clown therapy; the result is not statistically significant (Table 3). Q-test shows statistically significant ( $p = 0.045$ ) and high grade heterogeneity ( $I^2 = 62.78\%$ ).

### Child and Parent Anxiety

One study (57) evaluated the effect of clown therapy for child-perceived anxiety during and after the procedure. The authors did not observe a statistically significant difference between intervention and control group. The same study evaluated the effect of clown therapy for parent-perceived anxiety, again during and after the procedure; similarly, no statistically significant difference was observed.

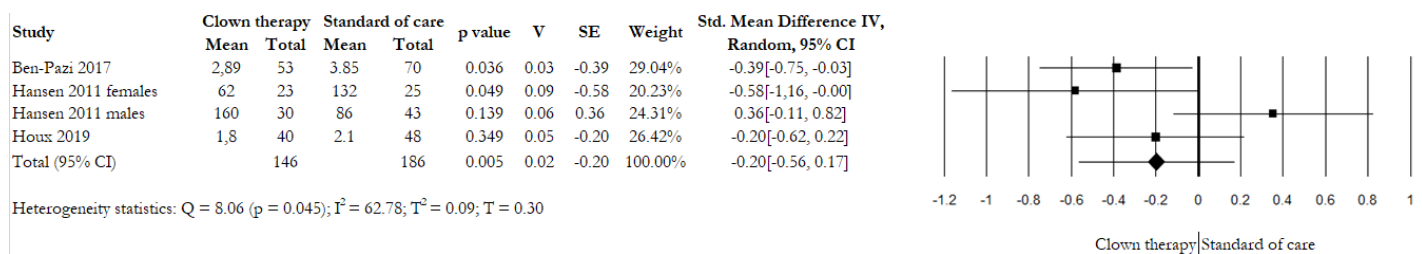


Table 3: Procedural pain in children with cerebral palsy - clowning vs. standard of care.

### Sensitivity analysis

Given the presence of an outlier study, a sensitivity analysis was performed by performing a meta-analysis after removing it.

In this way the aggregate SMD is -0.36 (95% CI: -0.61, -0.11) in favour of clown therapy; the result is statistically significant (Table 4).

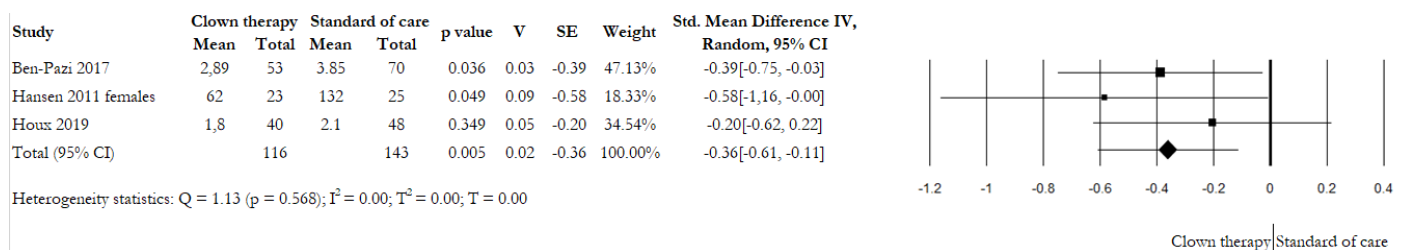


Table 4: Sensitivity analysis – removal of outlier study.

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## Additional analysis

**Sex:** Two studies (56,57) presented results as a function of participant sex but a quantitative synthesis could not be performed because one (57) did not make explicit, for the same sex, the number of sessions in which clown therapy or the standard of care was applied. The corresponding author was contacted for this information but to no avail. In one study (56) clown therapy was effective in reducing the mean duration of crying in female participants; the result is statistically significant; in male participants the mean duration of crying was longer with clown therapy; the result is not statistically significant. In the other study (57) both sexes benefited from the intervention, females to a greater extent than males; the results are not statistically significant.

**Age:** One study (57) found a greater effect of the intervention for children at least 9 years old; the result was not statistically significant.

**Severity of cerebral palsy:** One study (56) observed a wider benefit of clown therapy in

participants with quadriplegia, in another (57) no difference was found between children who could or could not walk. For both studies the results were not statistically significant.

**Level of cognitive impairment:** One study (57) assessed the benefit of the intervention according to the presence or absence of cognitive impairment; it was similar for both types of participants; the result was not statistically significant.

## Publication bias

The funnel plot was not inspected as it was of little use in the case of a small number of studies. For an objective assessment of the risk of bias, Egger's test (intercept = 0.56,  $t = 0.09$ ,  $p = 0.935$ ) and Begg and Mazumdar's test (Kendall's tau = 0.00,  $p = 1$ ) were used. The result of both tests, statistically not significant, suggests a minimal impact of publication bias.

## Summary of results

The quality of evidence assessed with the GRADE instrument was very low. The summary of results is shown in Table 5.

Effectiveness of clown therapy on procedural pain in children with cerebral palsy.

Clown therapy compared to control for procedural pain and anxiety in children, anxiety in parents

Patient or population: children with cerebral palsy undergoing potentially algogenic diagnostic or therapeutic procedures

Setting: any

Intervention: clown therapy

Comparison: standard of care

Outcome	Anticipated absolute effects* (95% CI)		N° of sessions (studies)	Certainty of the evidence (GRADE)	Comments**
	Risk with standard of care	Risk with clown therapy			
Children procedural pain	-	The mean level of procedural pain with clown therapy was 0.36 standard deviation lower (0.58 to 0.14 lower).	332 (2 qRCTs, 1 nRCT)	⊕⊕⊕⊕ Very low <sup>a,b,c</sup>	This result equates to a moderate difference in favor of clown therapy.
Children anxiety	-	-	47 (1 nRCT)	-	This outcome was assessed in one study only.
Parents anxiety	-	-	85 (1 nRCT)	-	This outcome was assessed in one study only.

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

\*\*0.2 represents a small difference, 0.5 a moderate difference and 0.8 a large difference.

CI: confidence interval; SMD: standardized mean difference; qRCT: quasi randomized controlled trial; nRCT: non randomized controlled trial

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

<sup>a</sup> Downgraded once for serious study limitations: trials had some concerns/high risk of bias.

<sup>b</sup> Downgraded once for suspicion of publication bias.

<sup>c</sup> Downgraded once for imprecision: analysis based on < 200 participants per group.

Table 5: Summary of Findings.

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## DISCUSSION

Our study aimed to measure the effectiveness of clown therapy compared with usual care on the procedural pain of children with CP. The included studies all focused on pain from intramuscular injection of botulinum toxin. This treatment is among those planned for children with CP and is the most widely used, effective, and safe method of reducing pain, spasticity, deformity, and improving mobility (14,21,61-63). It usually involves one or more injections into the target muscles (64); the therapeutic effect lasts 3-6 months, after which the injections need to be replicated (64,65). Although the procedure is short-lived, pain may occur during electrical muscle stimulation, puncture, and botulinum toxin inoculation (66). Judicious selection of sedative and analgesic agents and implementation of specific intramuscular injection guidance techniques (ultrasound, electrical stimulation, electromyography) are essential to reduce procedural pain and related anxiety in children with cerebral palsy (67,68). However, the use of preventive treatments such as nitrous oxide and anaesthetic cream seems effective for only half of children (66); hence the need for the contribution of non-pharmacological interventions, including distraction techniques such as clown therapy or play therapy (61,67,69-71). In children with CP, clown therapy appears to have good potential to help reduce procedural pain from intramuscular injection of botulinum toxin. The review highlighted that the intervention has an effect, albeit small (SMD = -0.2), on the symptom; on the other hand, given the rather low quality of the evidence, it is possible that the actual effect is very different from that estimated. The results should be viewed with great caution because of the few studies with low numbers of participants ( $n = 164$ ) and important methodological limitations resulting in low statistical

power and high heterogeneity among studies. Several critical points represent sources of heterogeneity: (a) the age range (0-18 years) of participants covers the entire pediatric range; (b) not all individuals had CP; (c) the degree of severity of CP nor the level of cognitive impairment was not always reported; (d) not all children were at their first experience of botulinum toxin injection; (e) studies do not make explicit whether children had previous experience of other needle procedures; (f) the number of injections per session was variable depending on the participant's disease characteristics. The session could (56,57) or could not (55) be preceded by the administration of sedative or analgesic agents. Clown therapy was performed by one (55,56) up to three (57) clown doctors, of undisclosed gender (except in one study (56) where it was specified to be a woman). Expertise and experience in the field was not described except generically, as were the distraction techniques applied. The standard of care could consist of comfort, attention and positive reinforcement from parents and/or care staff or include the provision of alternative distraction techniques. The instruments used for pediatric pain assessment were heterogeneous and sometimes improperly implemented. Specifically: 1) pediatric pain assessment scales are not effectively validated for children with intellectual disability, who make up a large proportion of those with cerebral palsy, or for children undergoing sedation, as was the case for most of the subjects analyzed by one study [55]; 2) one study used the FLACC scale on a sample of children from 0 to 15 years of age [56], but this instrument is validated for younger children, from 2 months to 7 years of age; 3) in two studies, the pain perceived by children during the procedure is also assessed according to the parent's perception [54, 56], and in one, pain is measured indirectly by quantifying

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the duration of crying of young patients after the first injection [55]. There is no doubt that the child's ability to comply with potentially painful repeated clinical procedures depends on gender, age, temperament, previous adverse experiences, and coping style (72). These variables may act as moderators of the effect of clown therapy; the same can be said of the child's personal sense of humor, which involves affective, social and cognitive processes and whose complexity may act as a barrier against the methodological rigor of studies (73). The results obtained from our study are consistent with those of previous systematic reviews that have evaluated the effect of clown therapy in children without CP (37-42): the intervention may be useful in reducing procedural pain. Furthermore, as evidenced by a pilot study (74) aimed at understanding the effects of clown therapy on children with physical, cognitive or developmental disabilities and undergoing long-term rehabilitation therapy, the intervention manifests an overall positive effect on their mood and well-being even with severe disabilities. Parents, caregivers, physicians and nurses are in favour of the integration of clown therapy in health care settings (55,57,75,76) also because, compared to other distraction techniques, the clown can adapt its performance according to the child's cognitive development within a non-demanding approach (72). The intervention also appears to be cost-effective (77). Against these advantages, in the included studies the clown was unfortunately only available on certain days and times.

## Research implications

In order to achieve greater certainty about the efficacy of the intervention, further studies with larger samples, higher methodological quality, and low risk of bias are needed. These studies should also address the effect of the intervention on other potentially

algogenic procedures these children undergo, such as physiotherapy, or corrective treatments such as orthotics or orthopaedic surgery. Due to the nature of the intervention, it was not possible to achieve blindness of the participants and health workers; however, there would be ways to blind the assessor, for example by filming the procedure and hiding the presence of the clown doctor (78). Clown therapy appears more effective in the female sex. Sensitivity analysis would seem to confirm this hypothesis, as by removing the outlier study, involving only male participants, the effect size increases and becomes statistically significant. However, this fluctuation in results with few studies with small samples could be the result of chance; the hypothesis that sex acts as a moderator of the intervention effect would therefore need to be confirmed by further research. The effect of the intervention seems to be age-dependent, but perhaps it would be more important to know for which age group clown therapy reaches its maximum effectiveness. It would also be important to know if the benefit changes according to the level of cognitive impairment or to the degree of severity of the disease. Child and parent anxiety has only been analyzed in one study (57), which found no statistically significant differences between the two groups. However, this result may have been affected by the synergistic effect of low pre-session anxiety and the prior use of sedatives and analgesics. It would be important to conduct further research on the assessment of anxiety, as it is closely related to procedural pain and more present in children with intellectual disability (29), a condition that severely affects 26.7% of individuals with CP (79). No study has used coulrophobia (or "fear of clowns") as an exclusion criterion; however, it would be interesting to study its impact in the pediatric population with future research. Another suggestive question concerns the

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effect a pediatric physician or pediatric nurse might have compared to that of a clown doctor if they wore a clown costume and had a joking and funny manner.

## Limits

The very low quality of the evidence and the high degree of heterogeneity among studies raise some concerns about the reliability and external validity of the emerging results. In addition, the differing manner in which the results were presented in the included studies meant that the data pull common to all and available for the meta-analysis was suboptimal, resulting in an inaccurate calculation of the effect size. Finally, the Egger's test and the Begg and Mazumdar test were used to assess the risk of publication bias; although both tests were not statistically significant, suggesting a minimal impact of publication bias, they are not very powerful in the case of a small number of studies.

## CONCLUSIONS

The review highlighted encouraging results on the effect of clown therapy for procedural pain from intramuscular injection of botulinum toxin in children with CP. However, the certainty/quality of the available evidence is very low, so the results should be considered with due caution. Because of this and pending further studies that overcome the current methodological limitations, it is not possible to provide a definitive judgement on the benefit of the intervention. Future research should explore more thoroughly whether clown therapy is more effective for the female sex or for a specific age group and whether it varies according to the degree of severity of CP or the level of intellectual disability. In addition, further studies should be promoted that evaluate the intervention's effect on other potentially algogenic procedures or treatments, such as

physiotherapy, orthotics, or orthopedic surgery, or that compare it with other distraction techniques (e.g., iPads, use of virtual reality).

## REFERENCES

- Centers for Disease Control and Prevention [Internet]: CDC, c2022. Cerebral palsy; 2022 May 2 [cited 2022 Jun 25]. Available from: <https://www.cdc.gov/ncbddd/cp/facts.html>; 2022
- Morgan C, Fahey M, Roy B, Novak I. Diagnosing cerebral palsy in full-term infants. *J Paediatr Child Health* 2018;54(10):1159-64. doi: 10.1111/jpc.14177.
- Colver A, Fairhurst C, Pharoah PO. Cerebral palsy. *Lancet* 2014;383(9924):1240-9. doi: 10.1016/S0140-6736(13)61835-8
- Maenner MJ, Blumberg SJ, Kogan MD, Christensen D, Yeargin-Allsopp M, Schieve LA. Prevalence of cerebral palsy and intellectual disability among children identified in two U.S. National Surveys, 2011–2013. *Ann Epidemiol* 2016; 26(3):222–6. doi: 10.1016/j.annepidem.2016.01.001
- Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. 2013. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. *Dev Med Child Neurol* 2013;55(6): 509–519. doi: 10.1111/dmcn.12080
- Reddihough D. Cerebral palsy in childhood. *Aust Fam Physician* 2011; 40(4): 192–6. PMID: 21597527
- Van Naarden Braun K, Doernberg N, Schieve L, Christensen D, Goodman A, Yeargin-Allsopp M. (2016). Birth Prevalence of Cerebral Palsy: A Population-Based Study.

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- Pediatrics 2016; 137(1): 1–9.  
<https://doi.org/10.1542/peds.2015-2872>
8. Wimalasundera N, Stevenson VL. Cerebral palsy. *Pract Neurol* 2016; 16(3): 184-94.
  9. Agarwal A, Verma I. Cerebral palsy in children: an overview. *J Clin Orthop Trauma* 2012;3(2):77–81.  
<https://doi.org/10.1016/j.jcot.2012.09.001>
  10. Graham D, Paget SP, Wimalasundera N. Current thinking in the health care management of children with cerebral palsy. *Med J Aust* 2019;210(3):129-35.
  11. Novak I, Hines M, Goldsmith S, Barclay R. Clinical prognostic messages from a systematic review on cerebral palsy. *Pediatrics* 2012; 130(5):e1285–e1312.  
<https://doi.org/10.1542/peds.2012-0924>
  12. Penner M, Xie, WY, Binopal N, Switzer L, Fehlings D. Characteristics of pain in children and youth with cerebral palsy. *Pediatrics* 2013; 132(2):e407–13.  
<https://doi.org/10.1542/peds.2013-0224>
  13. Rabach I, Peri F, Minute M, Aru E, Lucafò M, Di Mascio A, Cozzi G, Barbi E. (2019). Sedation and analgesia in children with cerebral palsy: a narrative review. *World J Pediatr* 2019;15(5):432–40.  
<https://doi.org/10.1007/s12519-019-00264-0>
  14. Cortellazzi P, Lamperti M, Minati L, Falcone C, Pantaleoni C, Caldiroli D. Sedation of neurologically impaired children undergoing MRI: a sequential approach. *Paediatr* 2007; 17(7):630–6. <https://doi.org/10.1111/j.1460-9592.2006.02178.x>
  15. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, Dan B, Jacobsson. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007;109:8–14. PMID: 17370477
  16. Engel JM, Jensen MP, Hoffman AJ, Kartir D. Pain in persons with cerebral palsy: extension and cross validation. *Arch Phys Med Rehabil* 2003; 84(8): 1125–8. doi: 10.1016/s0003-9993(03)00263-6
  17. Parkinson KN, Gibson L, Dickinson HO, Colver AF. Pain in children with cerebral palsy: a cross-sectional multicentre European study. *Acta Paediatr* 2010; 99(3): 446-51. doi: 10.1111/j.1651-2227.2009.01626.x
  18. Parkinson KN, Dickinson HO, Arnaud C, Lyons A, Colver A, SPARCLE group. Pain in young people aged 13 to 17 years with cerebral palsy: cross-sectional, multicentre European study. *Arch Dis Child* 2013; 98(6): 434–40. doi: 10.1136/archdischild-2012-303482.
  19. McKearnan KA, Kieckhefer GM, Engel JM, Jensen MP, Labyak S. Pain in children with cerebral palsy: a review. *J Neurosci Nurs* 2004; 36(5): 252–9. doi: 10.1097/01376517-200410000-00004
  20. Penner M, Davis WH, Wing K, Bemenderfer T, Waly F, Anderson RB. The Infinity Total Ankle System: Early Clinical Results With 2- to 4-Year Follow-up. *Foot Ankle Spec* 2019;12(2), 159–66.  
<https://doi.org/10.1177/1938640018777601>
  21. Ostojic K, Paget SP, Morrow AM. Management of pain in children and adolescents with cerebral palsy: a systematic review. *Dev Med Child Neurol* 2019; 61, 315–21. doi: 10.1111/dmcn.14088
  22. Roscigno CI. Addressing spasticity-related pain in children with spastic cerebral palsy.

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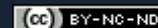
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- The J Neurosci Nurs 2002; 34(3), 123–33. doi: 10.1097/01376517-200206000-00005
23. Castle K, Imms C, Howie L. Being in pain: a phenomenological study of young people with cerebral palsy. *Dev Med Child Neurol* 2007; 49(6):445-9. doi: 10.1111/j.1469-8749.2007.00445
  24. Engel JM, Petrina TJ, Dudgeon BJ, McKearnan KA. Cerebral palsy and chronic pain: a descriptive study of children and adolescents. *Phys Occup Ther Pediatr* 2005; 25(4):73-84. doi: 10.1300/j006v25n04\_06.
  25. Hadden KL, von Baeyer CL. Pain in children with cerebral palsy: common triggers and expressive behaviours. *Pain* 2002; 99(1-2): 281–8. doi: 10.1016/s0304-3959(02)00123-9
  26. Nolan JI, Chalkiadis GA, Low J, Olesch CA, Brown TC. Anaesthesia and pain management in cerebral palsy. *Anaesthesia* 2000; 55(1): 32–41. doi: 10.1046/j.1365-2044.2000.01065.x
  27. Breau LM, Camfield CS, McGrath PJ, Finley GA. The incidence of pain in children with severe cognitive impairments. *Arch Pediatr Adolesc Med* 2003; 157(12):1219–26. <https://doi.org/10.1001/archpedi.157.12.1219>
  28. Fein JA, Zempsky WT, Cravero JP, Committee on Pediatric Emergency Medicine and Section on Anesthesiology and Pain Medicine, American Academy of Pediatrics. Relief of pain and anxiety in pediatric patients in emergency medical systems. *Pediatrics* 2012; 130(5):e1391-405. doi: 10.1542/peds.2012-2536
  29. Pascolo P, Peri F, Montico M, Funaro M, Parrino R, Vanadia F, Rusalen F, Vecchiato L, Benini F, Congedi S, Barbi E, Cozzi G. Needle-related pain and distress management during needle-related procedures in children with and without intellectual disability. *Eur J Pediatr* 2018;177(12), 1753-60. doi: 10.1007/s00431-018-3237-4
  30. Trottier ED, Doré-Bergeron MJ, Chauvin-Kimoff L, Baerg K, Ali S (2019) Managing pain and distress in children undergoing brief diagnostic and therapeutic procedures. *Paediatr Child Health* 2019;24(8):509-35. doi: 10.1093/pch/pxz026
  31. Pancekauskaitė G, Jankauskaitė L (2018) Paediatric pain medicine: pain differences, recognition and coping acute procedural pain in paediatric emergency room. *Medicina (Kaunas)* 2018;54(6):94. doi: 10.3390/medicina54060094
  32. Ali S, McGrath T, Drendel AL, Amy LDO. An evidence based approach to minimizing acute procedural pain in the emergency department and beyond. *Pediatr Emerg Care* 2016;32(1):36-42; quiz 43-4. doi: 10.1097/PEC.0000000000000669
  33. Ostojic K, Paget S, Kyriagis M & Morrow A. (2020). Acute and chronic pain in children and adolescents with cerebral palsy: prevalence, interference, and management. *Arch Phys Med Rehabil* 202;101(2):213-9. doi: 10.1016/j.apmr.2019.08.475
  34. Cooke MW. UK Ambulance Service Clinical Practice Guidelines 2006; 2006 Oct [cited 2022 Sept 16]. Available from: [http://www.ambo.com.au/download/uk\\_guidelines\\_2006.pdf](http://www.ambo.com.au/download/uk_guidelines_2006.pdf).
  35. Chen E, Joseph MH, Zeltzer LK. Behavioral and cognitive interventions in the treatment of pain in children. *Pediatr Clin North Am*

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- 2000;47(3):513-25. doi: 10.1016/s0031-3955(05)70223-6
36. Berk LS, Tan SA, Fry WF, Napier BJ, Lee JW, Hubbard RW, Lewis JE, Eby WC. Neuroendocrine and stress hormone changes during mirthful laughter. *Am J Med Sci* 1989;298(6):390-6. doi: 10.1097/00000441-198912000-00006
37. Ding Y, Yin H, Wang S, Meng Q, Yan M, Zhang Y, Chen L. Effectiveness of clown intervention for pain relief in children: A systematic review and meta-analysis. *J Clin Nurs* 2022. doi: 10.1111/jocn.16195. Online ahead of print
38. Fusetti V, Re L, Pigni A, Tallarita A, Cilluffo S, Caraceni AT, Lusignani M. Clown therapy for procedural pain in children: a systematic review and meta-analysis. *Eur J Pediatr* 2022;181(6):2215-25. doi: 10.1007/s00431-022-04440-9
39. Könsgen N, Polus S, Rombey T, Pieper D. Clowning in children undergoing potentially anxiety-provoking procedures: a systematic review and meta-analysis. *Syst Rev* 2019;8(1):178. doi: 10.1186/s13643-019-1095-4
40. Lopes-Junior LC, Silveira DS, Olson K, Bomfim EO, Veronez LC, Santos JC, Lima RA. Clown intervention on psychological stress and fatigue in pediatric patients with cancer undergoing chemotherapy. *Cancer Nurs* 2020;43(4):290-9. doi: 10.1097/NCC.0000000000000690
41. Sridharan K, Sivaramakrishnan G. Therapeutic clowns in pediatrics: a systematic review and meta-analysis of randomized controlled trials. *Eur J Pediatr* 2017;176(5):681-2. doi: 10.1007/s00431-017-2889-9.
42. Uçun Y, Küçük L. Terapötik Palyaço Müdahalesinin Çocukların Ruh Sağlığına Etkisi: Sistematik Derleme. *Jaren* 2020;6(3):598-609. doi:10.5222/jaren.2020.93584
43. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi: 10.1136/bmj.l4898.
44. McGuinness, LA, Higgins, JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Res Syn Meth* 2021;12(1):55-61. doi:10.1002/jrsm.1411
45. Cohen J. *Statistical power analysis for the behavioral sciences*. 2nd ed. Hillsdale: Lawrence Erlbaum Associates;1998.
46. Cochran WG. The comparison of percentages in matched samples. *Biometrika* 1950; 37(3/4), 256-66. PMID: 14801052
47. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557
48. Calderón MA, Boyle RJ, Penagos M, Sheikh A. Immunotherapy: the meta-analyses. What have we learned? *Immunol Allergy Clin North Am* 2011;31(2):159-73, vii. doi: 10.1016/j.iac.2011.02.002.
49. Sterne JA, Egger M. Funnel plots for detecting bias in metaanalysis: guidelines on choice of axis. *J Clin Epidemiol* 2001;54(10):1046-55. doi: 10.1016/s0895-4356(01)00377-8

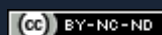
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50. Duval S, Tweedie R. Trim and fill: a simple funnel-plotbased method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56(2):455-63. doi: 10.1111/j.0006-341x.2000.00455.x.
51. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in metaanalysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629-34. doi: 10.1136/bmj.315.7109.629.
52. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50(4):1088-101. PMID: 7786990
53. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi:10.1136/bmj.n71
54. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011;64(4):401-6. doi: 10.1016/j.jclinepi.2010.07.015
55. Ben-Pazi H, Cohen A, Kroyzer N, Lotem-Ophir R, Shvili Y, Winter G, et al. Clown-care reduces pain in children with cerebral palsy undergoing recurrent botulinum toxin injections-A quasi-randomized controlled crossover study. *PLoS One* 2017;12(4):e0175028. doi: 10.1371/journal.pone.0175028
56. Hansen LK, Kibaek M, Martinussen T, Kragh L, Hejl M. Effect of a clown's presence at botulinum toxin injections in children: a randomized, prospective study. *J Pain Res* 2011;4:297-300. doi: 10.2147/JPR.S23199
57. Houx L, Dubois A, Brochard S, Pons C. Do clowns attenuate pain and anxiety undergoing botulinum toxin injections in children?. *Ann Phys Rehabil Med* 2020;63(5):393-9. doi: 10.1016/j.rehab.2018.12.004
58. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs* 1997;23(3):293-7. PMID: 9220806
59. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018;27(6):1785-1805. doi: 10.1177/0962280216669183
60. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135. doi: 10.1186/1471-2288-14-135
61. Copeland L, Edwards P, Thorley M, Donaghey S, Gascoigne-Pees L, Kentish M, et al. Botulinum toxin A for nonambulatory children with cerebral palsy: a double blind randomized controlled trial. *J Pediatr* 2014;165(1):140-6.e4. doi: 10.1016/j.jpeds.2014.01.050.
62. Whelan MA, Delgado MR. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the quality standards subcommittee of the american academy of neurology and the practice committee of the child neurology society. *Neurology* 2010;75(7):669. doi: 10.1212/WNL.0b013e3181ec670b

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63. Multani I, Manji J, Hastings-Ison T, Khot A, Graham K. Botulinum toxin in the management of children with cerebral palsy. *Paediatr Drugs* 2019;21(4):261-81. doi: 10.1007/s40272-019-00344-8.
64. Druschel C, Althuis HC, Funk JF, Placzek R. Off label use of botulinum toxin in children under two years of age: a systematic review. *Toxins (Basel)* 2013;5(1):60-72. doi: 10.3390/toxins5010060.
65. Novak I, McIntyre S, Morgan C, Campbell L, Dark L, Morton N, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol* 2013;55(10):885-910. doi: 10.1111/dmcn.12246.
66. Brochard S, Blajan V, Lempereur M, Le Moine P, Peudenier S, Lefranc J, et al. Effectiveness of nitrous oxide and analgesic cream (lidocaine and prilocaine) for prevention of pain during intramuscular botulinum toxin injections in children. *Ann Phys Rehabil Med* 2009;52(10):704-16. doi: 10.1016/j.rehab.2009.09.001
67. Cantador-Hornero M, Jiménez-Espuch P, de Torres-García I, Contreras-Jiménez M, Martínez-Mezo G, Morales de los Santos J, et al. Sedation analgesia protocol for the injection of botulinum toxin a in cerebral palsy. *An Pediatr (Engl Ed)* 2019;91(5):317-27. doi: 10.1016/j.anpedi.2018.12.018
68. Heinen F, Desloovere K, Schroeder A, Berweck S, Borggraefe I, Van Campenhout A, et al. The updated European Consensus 2009 on the use of botulinum toxin for children with cerebral palsy. *Eur J Paediatr Neurol* 2010;14(1):45-66. doi: 10.1016/j.ejpn.2009.09.005
69. Bakheit A. Botulinum toxin in the management of childhood muscle spasticity: comparison of clinical practice of 17 treatment centres. *Eur J Neurol* 2003;10(4):415-9. doi: 10.1046/j.1468-1331.2003.00619.x.
70. Brochard S, Blajan V, Lempereur M, Garlantezec R, Houx L, Le Moine P, et al. Determining the technical and clinical factors associated with pain for children undergoing botulinum toxin injections under nitrous oxide and anesthetic cream. *Eur J Paediatr Neurol* 2011;15(4):310-5. doi: 10.1016/j.ejpn.2010.12.006
71. Zier JL, Rivard PF, Krach LE, Wendorf HR. Effectiveness of sedation using nitrous oxide compared with enteral midazolam for botulinum toxin A injections in children. *Dev Med Child Neurol* 2008;50(11):854-8. doi: 10.1111/j.1469-8749.2008.03069.x.
72. Pérez-Aranda A, Hofmann J, Feliu-Soler A, Ramírez-Maestre C, Andrés-Rodríguez L, Ruch W, et al. Laughing away the pain: A narrative review of humour, sense of humour and pain. *Eur J Pain* 2019;23(2):220-33. doi: 10.1002/ejp.1309
73. Kurudirek F, Arikan D, Sarialioğlu A. Effects of therapeutic clowning on pain and anxiety during venous blood sampling in Turkey: Randomised controlled trial. *J Spec Pediatr Nurs* 2021;26(4):e12352. doi: 10.1111/jspn.12352
74. Kingsnorth S, Blain S, McKeever P. (2011). Physiological and emotional responses of disabled children to therapeutic clowns: a pilot study. *Evid Based Complement Alternat Med* 2011;2011:732394. doi: 10.1093/ecam/neq008

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75. Battrick C, Glasper EA, Prudhoe G, Weaver K. Clown humour: the perceptions of doctors, nurses, parents and children. *J Child Young People Nurs* 2007;1(4), 174-9. doi:10.12968/jcyn.2007.1.4.24403
76. Koller D, Gryski C. The life threatened child and the life enhancing clown: towards a model of therapeutic clowning. *Evid Based Complement Alternat Med* 2008;5(1):17-25. doi: 10.1093/ecam/nem033
77. Javed T, Khan AS, Jarral NA, Taqi Z, Raza M, Shahid Z. Medical Clowning: A Cost-Effective Way to Reduce Stress Among Children Undergoing Invasive Procedures. *Cureus* 2021;13(10):e18886. doi: 10.7759/cureus.18886
78. Felluga M, Rabach I, Minute M, Montico M, Giorgi R, Lonciari I, et al. A quasi randomized-controlled trial to evaluate the effectiveness of clown therapy on children's anxiety and pain levels in emergency department. *Eur J Pediatr* 2016;175(5):645-50. doi: 10.1007/s00431-015-2688-0.
79. Cummins D, Kerr C, McConnell K, Perra O. Risk factors for intellectual disability in children with spastic cerebral palsy. *Arch Dis Child* 2021;106(10):975-80. doi: 10.1136/archdischild-2020-320441.



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