Cochrane Response

Protocol for a guideline on palliative care in children and young people

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1. Project description

The Association for Paediatric Palliative Medicine (APPM) aims to undertake a series of systematic reviews in order to produce a clinical practice guideline on the management of symptoms in infants, children and young people (ICYP) with palliative care needs. This work builds on previous guidance published by NICE (1).

A series of PICO questions have been agreed by the APPM guideline development group which cover a range of topics. Following a prioritization exercise, the APPM selected three topics: agitation, gut failure and seizures.

2. Methods overview

2.1. Population, Intervention, Comparisons, Outcomes, Study design (PICOS)

Agitation

Review question	What pharmacological and non-pharmacological interventions are effective for the management of agitation in infants, children and young people with palliative care needs?
Population	Infants, children and young people (up to 19 years) with life limiting conditions who may experience or be at risk of experiencing agitation during their illness and benefiting from a palliative care approach
Intervention	Pharmacological • Benzodiazipines • Chloral hydrate • Propranolol • Levomepromazine • Oxygen • Gabapentin, pregablin • Risperidone, Haloperidone, Olanzepine, clonidine • SSRI, SNRI or tricyclics • Methadone • Cannaboids Non-pharmacological, such as: • Complementary therapies- acupuncture, reflexology • Play • Art therapy • Animal therapy • Music • Hypnotherapy • Guided imagery • Psychology- CBT • Recognition of emotional and situation triggers • Trigger avoidance, music therapy

Comparison	• Placebo, • No treatment / usual care • Cross comparison between any of the above (within group and between group) • Combinations of the above • Routes of administration (same drug or same drug class)
Outcomes	• Efficacy • Safety • Satisfaction

Gut failure

Review question	What pharmacological and non-pharmacological interventions are effective for the practical management of the effects of gut failure symptoms in infants, children and young people with palliative care needs?
Population	Infants, children and young people (up to 19 years) with life limiting conditions and gut failure, benefiting from a palliative care approach
Intervention	Pharmacological • Omeprazole, lansoprazole, Ranitidine, Famotidine, Domperidone, Gaviscon • Metoclopramide, erythromycin, levomepromazine, cyclizine, ondansetron, granestron, stemetil, nabilone, other cannabinoids, appreprintant, baclofen. • Gabapentin, pregabalin, amitriptyline, clonidine, SSRI- Fluoxetine, Duloxetine, diazepam, midazolam, lorazepam, clonazepam, clobazam, chloral hydrate. • Opiates (morphine, fentanyl, oxycodone, dihydrocodiene and buprenorphine) methadone, ketamine. • Lactulose, Movicol, enaemas, ducosate, picosulfate, senna. • Alimemazine, octreotide, Neostigmine, pyridostigmine, cyproheptadine, H. Pylori treatment. • Over-counter remedies: Peppermint tea/oil • PN/TPN, home TPN/PN, fluids IV/SC Non-pharmacological • Perastigmen treatment, Farrell bag, flatus tube, replogle tube, ng feeding, jej feeding, venting. • Hydrolysed formulaes, alterations of feeding regimen, blended diet, exclusion diets, feed thickeners, carobel. • Psychological intervention, distraction therapy, music therapy, art therapy, play therapy, complementary therapies, acupuncture, hydrotherapy, reflexology, abdominal massage. Environmental triggers Place of care, access to tissue viability, bed and seating cushions, mattresses including airflow, oral care and hygiene, over feeding, formula osmolarity, feeding rate reduction.

	Surgical/procedural Botox, celiac plexus block, gastrostomy, jejunostomy, fundoplication, defunctioning colostomy, gut resection, transplant, PN, central line, midlines, PICC lines, Roux en y, stenting, dilatation
Comparison	• Placebo, • No treatment / usual care • Cross comparison between any of the above (within group and between group) • Combinations of the above • Routes of administration (same drug or same drug class)
Outcomes	• Efficacy • Safety • Satisfaction

Seizures

Review question	What pharmacological and non-pharmacological interventions are effective for the management of seizures in infants, children and young people with palliative care needs?
Population	Infants, children and young people (up to 19 years) with life limiting conditions and complex seizures, benefiting from a palliative care approach
Intervention	Pharmacological Midazolam, clobazam, clonazepam, levetiracetam, Phenobarbital, diazepam, lorazepam, paraldehyde, steroids, Ketamine, CBD, Phenytoin Non-pharmacological Trigger avoidance, music therapy Environmental triggers, including sleep / pain/ agitation /constipation Information and support Surgery / radiotherapy/ VNS Ketogenic diet
Comparison	• Placebo, • No treatment / usual care • Cross comparison between any of the above (within group and between group) • Combinations of the above • Routes of administration (same drug or same drug class)
Outcomes	• Efficacy • Safety • Satisfaction

2.1.1. Study designs

Experimental and observational comparative studies were prioritised for inclusion, including:

- randomized controlled trials and quasi-randomized controlled trials
- non-randomized controlled trials
- controlled before and after studies
- interrupted time series studies
- historically controlled studies
- cohort studies with a control group
- case-control studies

Studies without a control group, including case reports, were not be included in the analysis, but the results were tabulated and presented in an appendix.

2.1.2. Subgroups

Relevant subgroups included: age, gender, and other comorbidities.

Given the limited amount of evidence, it was not possible to conduct subgroup analysis.

2.1.3. Publication characteristics

Unpublished studies and studies in press were considered for inclusion if they met the inclusion criteria; where data were not available or where data were not usable, this was stated in the report.

Abstracts without a full-text publication were also included if they met the inclusion criteria.

Non-English language papers were included if they met the inclusion criteria. Screening and data extraction was performed by a speaker of the language.

Ongoing studies were tabulated.

2.2. Search strategies

We aimed to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress).

2.2.1. Electronic search

We searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE (PubMed); EMBASE (OVID) and Psycinfo.

2.2.2. Searching other resources

We searched the reference lists of all relevant systematic reviews published within the search dates.

We also screened other potentially relevant published or unpublished data provided by the APPM guideline group.

2.3. Selection of studies

We used Distiller software (www.evidencepartners.com) for screening. Two review authors independently screened all citations and abstracts identified in the search. We will obtained full reports for potentially eligible studies and these were also independently screened by two review authors. We resolved any disagreements through a third reviewer or by discussion. Justifications for excluding full text reports from the review were documented and reported. We checked that

included studies were independent, and looked for multiple publications of the same study and ensure it was included only once (this is usually referred to as studyfication process).

2.4. Data extraction and management

We used Distiller software for data extraction. One reviewer extracted data using pre-tested data extraction forms. A second reviewer crosschecked the extracted data. We resolved any disagreements about data extraction by referring to the study report and by discussion.

For all studies, we extracted details on the authors, study date, population, age, country, interventions and outcomes reported.

We recorded the number of participants experiencing the event and the number analysed in each treatment group.

For trials randomly assigned using clusters (cluster-RCTs) we planned to extract the intra-cluster correlation coefficient (ICC) when available; and recorded the number of clusters per group, the total size of clusters per group and the unit of randomization (e.g. household or institution).

For observational studies, data collected the confounding factors considered in the analysis (if reported) and for the methods used to control for confounding. Because of the need to control for confounding, whenever available, we preferred to extract data for multiple effect estimates, as follows: on the number of people analysed, adjusted and unadjusted effect estimates with their respective measure of variance (standard error (SE), or 95% confidence interval (95%CI)), and the relevant confounding variables used to adjust the analysis. We also extracted raw data from contingency tables reporting the number of individuals with the outcome of interest (or prevalence rates) and the total number of individuals in the intervention and control groups, when available.

2.5. Assessment of risk of bias

One reviewer independently assessed the risk of bias of each included study, and a second reviewer crosschecked the assessment. Disagreements were resolved through discussion with a methodologist.

For RCTs or quasi-RCTs, we used the Cochrane Risk of Bias tool for RCTs (Higgins 2011).

For observational studies with a control group, we used the Cochrane Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) (Sterne 2016).

We considered the most important confounders to be age, sex, and co-interventions.

The results of the risk of bias assessments were summarised and we provided an evaluation of the overall risk of bias of the included studies. These assessments also assisted with GRADEing the evidence at the outcome level.

2.6. Measures of treatment effect

RCTs

If sufficient studies had been included, we would have evaluated treatment effects for continuous outcomes using mean differences (MDs), or standardised mean differences (SMD) for results across studies with outcomes that were conceptually the same, but measured in different ways.

In the event that studies presented dichotomous data (e.g. responder analyses), we would have used risk ratios (RRs). We would have calculated 95% confidence intervals (CIs) for the measures of

treatment effect. We planned on using Peto odds ratios (OR) with their respective 95% CIs to estimate effects for outcomes with rare events.

We would have undertaken meta-analyses only where meaningful, that is, when treatments, participants, and the underlying clinical questions were similar enough for pooling to make sense.

Observational studies

For observational studies, we had planned, where data permits, to combine adjusted point estimates using ORs and their 95% CIs in the first instance. If adjusted point estimates were not available, we planned to combine unadjusted estimates in the logarithm scale or the Relative Risk Reduction and its 95% confidence interval. We planned to use the DerSimonian and Laird random-effects method. When data could not be pooled, we reported results narratively. If both adjusted and unadjusted estimates were reported within a study, we planned to give preference to the estimate that adjusted for the most important confounders for the review.

2.7. Sensitivity analysis

If a study was of doubtful eligibility for the systematic review, appeared to be an outlier, or had missing data that were impossible to retrieve, we had intended to compare the results of analyses with and without the trial. However, there was only one trial for any comparison.

2.8. Summarising and interpreting results

We used the GRADE approach to interpret findings and create 'Summary of findings' tables following the GRADE handbook. These tables provide outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on the following outcomes rated as particularly important to patient-care and decision-making: effectiveness, safety, and satisfaction (specific outcomes to be decided with WHO).

Evidence certainty will be downgraded for the following reasons:

- Limitations in study design or execution (risk of bias)
- Inconsistency of results
- Indirectness of evidence
- Imprecision
- Publication bias

Data from observational studies can be upgraded for the following reasons:

- If the pooled estimates revealed a large magnitude of effect
- Dose-response gradient

The different levels of certainty that result from GRADEing the evidence will be interpreted as follows:

- **High certainty:** further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate certainty:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

- **Low certainty:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low certainty:** we are very uncertain about the estimate.

3. References

1. National Institute for Health and Care Excellence. (2016). End of life care for infants, children and young people with life-limiting conditions: planning and management. NICE guideline, NG61.

2. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2011.

3. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. bmj. 2016;355:i4919.