Cochrane Response

APPM guidelines
Q2. Agitation

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Summary

This systematic review was performed as part of an APPM guideline on "Symptom management in children and young people receiving palliative care"

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?

Selection criteria

See Agitation methodology report for the full systematic review protocol.

Population

CYP with life limiting conditions and benefiting from a palliative care approach. This might be defined by complexity, route of drug administration, place of care or phase of illness.

Intervention

- Pharmacological interventions
- Non-pharmacological interventions

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

Effectiveness, safety, and satisfaction.

Study design

Randomised controlled trials (RCTs) and observational comparative studies were prioritised for inclusion. Evidence from non-comparative studies was recorded; however, the results were not included in the GRADE Summary of Findings tables.

Methods

Search methods

MEDLINE (Ovid) and Embase (Ovid) and Cochrane CENTRAL (Wiley) were searched on April 6, 2021. All databases were searched from inception and no language restrictions were used. See Appendix 1 for search strategy details.

Data collection and analysis

Screening, data extraction and risk of bias assessments were performed in duplicate by two independent reviewers.

For the risk of bias assessments, we used the ROBINS-I tool for non-randomised studies (Sterne 2016).

Risk ratios (RRs) or odds ratios (ORs) and their 95% confidence intervals (CI) were calculated for dichotomous outcome data. Mean differences (MD) and their 95% CI were calculated for continuous outcomes.

Summarising and interpreting results

We used the GRADE approach to interpret findings and create 'Summary of findings' tables following the GRADE handbook (Schünemann 2019).

Search results

We retrieved a total of 790 records. After deduplication, 628 unique abstracts were screened. We retrieved the full text of 117 records and after screening excluded 116 records. One retrospective cohort study was identified for inclusion. In addition, two observational non comparative studies were also identified.

See Appendix 2 for PRISMA flowchart of the screening and study selection process, and Appendix 3 for list of excluded studies.

Included studies

See Characteristics of included studies table and Appendix 4 for full Risk of Bias assessments.

The risk of bias of all the included observational comparative study was considered at critical risk of bias overall due to confounding and selection bias.

Main results

Pharmaceutical interventions

1_Olanzapine vs risperidone

One retrospective study comparing olanzapine and risperidone was identified (Peled 2020). This is a retrospective study conducted in Israel with 43 children aged 0 to 20 years receiving treatment from the haemato-oncology service who had been evaluated by a child psychiatrist and had been treated with antipsychotic medication. See Summary of Findings, Characteristics of included studies and Forest plots.

Clinical global impression of change

Olanzapine may reduce CGI-I scores at reassessment compared with risperidone; however, the certainty of

the evidence is very low (MD -0.7; 95% CI -1.37 to -0.03; N = 43).

Adverse events

The treatment with olanzapine may have little to no impact on adverse events; however, the certainty of the evidence is very low (RR 0.96; 95% CI 0.24 to 3.77; N = 43).

Seven patients (four olanzapine- and three risperidone) experienced six different adverse events that were due to the treatment with olanzapine or risperidone.

Three of them had more than one side effect. However, most of the adverse events were reported to be mild (grade 1–2 evaluated by the CTCAE (2017). In spite of the mild side effect, three out of the seven discontinued antipsychotic medication due to these side effects.

2_Methotrimeprazine

In addition, we identified a single-arm cohort study (Hohl, 2013,) and one case series (Van Der Zwaan 2011) that described the use of methotrimeprazine. See Appendix 5 for a summary of the main results.

Non-pharmacological interventions

No studies were identified.

Overall certainty of the evidence

The certainty of the evidence was very low.

Outcomes were downgraded due to methodological limitations such as selection bias and/ or lack of adjustment for confounders. Outcomes were also downgraded due to imprecision as there were few events and participants and wide confidence intervals.

Although the evidence was not downgraded due to indirectness, it is important to note that the evidence derives from a single country, and this may limit the generalization of the results.

Indirect evidence

The Guideline Development Group also identified additional supporting indirect evidence that they considered useful to guide discussion around recommendations. A summary table is presented in Appendix 6.

Characteristics of included studies

Study details	Methods	Participants	Interventions	Outcomes measured in the study	Risk of bias summary
Ref ID 20 **Peled, 2020** **Israel** Clinical trial registration: not reported Conflict of interest: none stated Funding: none Contact details: nbenaroya@gmail.com	Study design: Retrospective cohort study Setting: Facility based Study dates: July 2010 - September 2017	Children aged 0-20 years, receiving treatment from the Haemato-oncology service who had been evaluated by a child psychiatrist and had been treated with antipsychotic medication N = 43 Age: mean (SD) 12.1 (5.2) years; range: 2.9 to 19.6 years Sex: 51% male, 49% female Health condition: leukaemia; lymphoma; brain tumour; extracranial embryonal tumour; bone marrow transplant	• Olanzapine - Mean dose 3.5 – 1.7 mg, number of doses, concentration, timing, route and setting not stated (n = 25) • Risperidone - Mean dose 0.8 – 0.9 mg, number of doses, concentration, timing, route and setting not stated (n = 18) The choice of drug was at the discretion of the treating psychiatrist	• Clinical global impression score • Adverse events due to treatment	ROBINS-I summary Critical risk of bias

Summary of Findings

SOF 1. Olanzapine versus risperidone for the management of agitation

Q2. Olanzapine versus risperidone for the management of agitation

Patient or population: Children aged 0-20 years, receiving treatment from the Haemato-oncology service who had been evaluated by a child psychiatrist and had been treated with antipsychotic medication

Setting: Israel

Intervention: Olanzapine

Comparison: Risperidone

Outcomes	Anticipated absolute effects* (95% CI)		Risk difference with olanzapine	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with risperidone	Risk with olanzapine					
Clinical global impression of change Assessed by psychiatrist; scores range from 1 (very much improved) through to 7 (very much worse) Follow-up: not reported	The mean clinical global impression of change was 3	MD 0.7 lower (1.37 lower to 0.03 lower)	-	P < 0.05	43 (1 observational study) [1]	⊕◯◯◯ VERY LOW [a, b]	Olanzapine may reduce CGI-I scores at reassessment compared with risperidone; however, the certainty of the evidence is very low

Outcomes	Anticipated absolute effects* (95% CI)		Risk difference with olanzapine	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with risperidone	Risk with olanzapine					
Adverse events due to treatment Follow-up: not reported	167 per 1000	160 per 1000 (40 to 628)	7 fewer per 1000 (from 127 fewer to 462 more)	RR 0.96 (0.24 to 3.77)	43 (1 observational study)	⨁◯◯◯ VERY LOW [a,b,d]	Olanzapine may have little to no impact on adverse events; however, the certainty of the evidence is very low. Seven patients (four olanzapine- and three risperidone) experienced six different adverse events that were due to the treatment with olanzapine or risperidone. Three of them had more than one side effect. However, most of the adverse events were reported to be mild (grade 1–2 evaluated by the CTCAE (2017). In spite of the mild side effect, three out of the seven discontinued antipsychotic medication due to these side effects.

*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).
CI: Confidence interval; RR: Risk ratio

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

1. Peled 2020

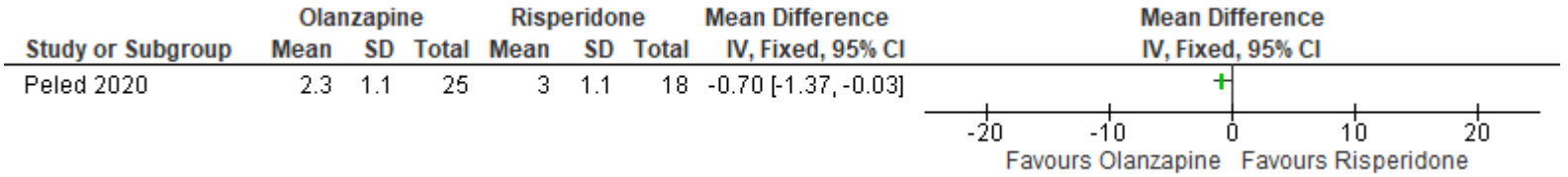
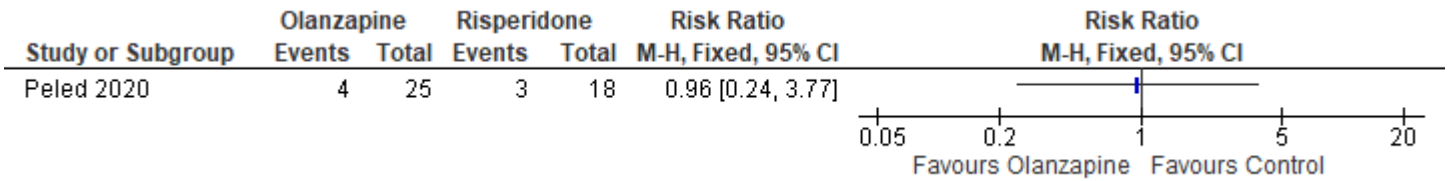
a. Downgraded 1 levels due to risk of bias: non-randomised retrospective study. The study was rated at critical risk due to confounding and selection bias. No adjustment for confounders was made.

b. Single study, inconsistency cannot be assessed

c. Downgraded 1 level due to imprecision: few participants

d. Downgraded 1 level due to imprecision: very wide confidence interval that incorporates the possibility of benefit and the possibility of harm and few participants and events

Forest plots

Outcome	Forest plots	Certainty of the evidence (GRADE)
Clinical global impression of change Assessed by psychiatrist; scores range from 1 (very much improved) through to 7 (very much worse) Follow-up: not reported [observational studies]		⊕◯◯◯ VERY LOW
Adverse events due to treatment Follow-up: not reported		⊕◯◯◯ VERY LOW

References

Included studies

Peled 2020

Peled, Orit, Lavan, Orly, Stein, Jerry, Vinograd, Inbal, Yahel, Anat, Valevski, Avi, Weizman, Abraham, Kimmel-Tamir, Ella, Apter, Alan, Fennig, Silvana, Yaniv, Isaac, Bernfeld, Yael, Benaroya-Milshtein, Noa 2020. Psychopharmacology in the Pediatric Oncology and Bone Marrow Transplant Units: Antipsychotic Medications Palliate Symptoms in Children with Cancer Journal of child and adolescent psychopharmacology, 30(8): 486-494.

Observational non-comparative studies

Hohl 2013

Hohl, Christopher M., Stenekes, Simone, Harlos, Michael S., Shepherd, Erin, McClement, Susan, Chochinov, Harvey Max 2013. Methotrimeprazine for the management of end-of-life symptoms in infants and children Journal of palliative care, 29(3): 178-85.

Van Der Zwaan 2012

Van Der Zwaan, Sanne, Blankespoor, Roos J., Wolters, Anton M. H., Creten, Caroline, Schieveld, Jan N. M., Leroy, Piet L. J. M. 2012. Additional use of methotrimeprazine for treating refractory agitation in pediatric patients Intensive Care Medicine, 38(1): 175-176.

Other references

Sterne 2016

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

Schünemann 2019

Schünemann HJ, Vist GE, Higgins JPT, Santesso N, Deeks JJ, Glasziou P et al. Interpreting results and drawing conclusions. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 6.0 edition. Available from www.training.cochrane.org/handbook: Cochrane, 2019: Chapter 15.

Declarations of interest

Cochrane Response, which is an evidence consultancy operated by The Cochrane Collaboration, was commissioned to perform this review for the WHO. All Cochrane Response authors declare no conflicts of interest.

All signed declarations of interest can be found on the following link: https://community.cochrane.org/organizational-info/people/conflict-interest/cet or on APPM website.

Acknowledgments

We thank Elise Cogo (Cochrane Response) for running the search strategy.

Appendix 1. Search strategy

MEDLINE (Ovid) Search Strategy (Revised April 24, 2021)

1. ADOLESCENT/ or MINORS/
2. (adolescen$ or teen$ or youth$ or young or juvenile? or minors or highschool$).mp,jw,nw.
3. exp CHILD/
4. (child$ or schoolchild$ or "school age" or "school aged" or preschool$ or pre-school* or toddler$ or kid? or kindergar$ or boy? or girl?).mp,jw,nw.
5. exp INFANT/
6. (infan$ or neonat$ or newborn$ or baby or babies).mp,jw,nw.
7. exp PEDIATRICS/ or exp PUBERTY/
8. (p?ediatric$ or pubert$ or prepubert$ or pubescen$ or prepubescen$).mp,jw,nw.
9. or/1-8
10. TERMINALLY ILL/
11. ((terminal$ or final or advance$ or incurable or life limit$) adj3 (ill$ or disease$ or condition$)).mp.
12. dying.mp.
13. (end adj3 life).mp.
14. ((approach$ or close$ or near$ or imminent$ or impending) adj3 death).mp.
15. (Body adj2 (shut? down or shutting down or deteriorat$)).mp.
16. (deathbed? or death bed? or passing away or passing on or expiring or expiration or syringe driver*).mp.
17. ((last or final) adj1 (hour$ or days$ or minute$)).mp.
18. (last year of life or LYOL or life$ end).mp.
19. (advance$ stage? or final stage? or end stage? or last stage? or late stage? or terminal stage?).mp.
20. ((advanced or late or last or end or final or terminal) adj phase$).mp.
21. RESUSCITATION ORDERS/
22. (resuscitat$ adj3 (policies or policy or order? or decision? or withhold$)).mp.

23. ADVANCE DIRECTIVES/

24. advance? directive?.mp.

25. LIVING WILLS/

26. living will?.mp.

27. TERMINAL CARE/

28. (terminal$ adj3 (care$ or caring)).mp.

29. PALLIATIVE CARE/

30. palliat$.mp.

31. HOSPICE CARE/

32. hospice?.mp.

33. or/10-32

34. PSYCHOMOTOR AGITATION/

35. (agitat$ or akathisia or restless$ or deliri$).mp.

36. DELIRIUM/

37. 34 or 35 or 36

38. 9 and 33 and 37

39. 33 and 37

40. limit 39 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")

41. 38 or 40

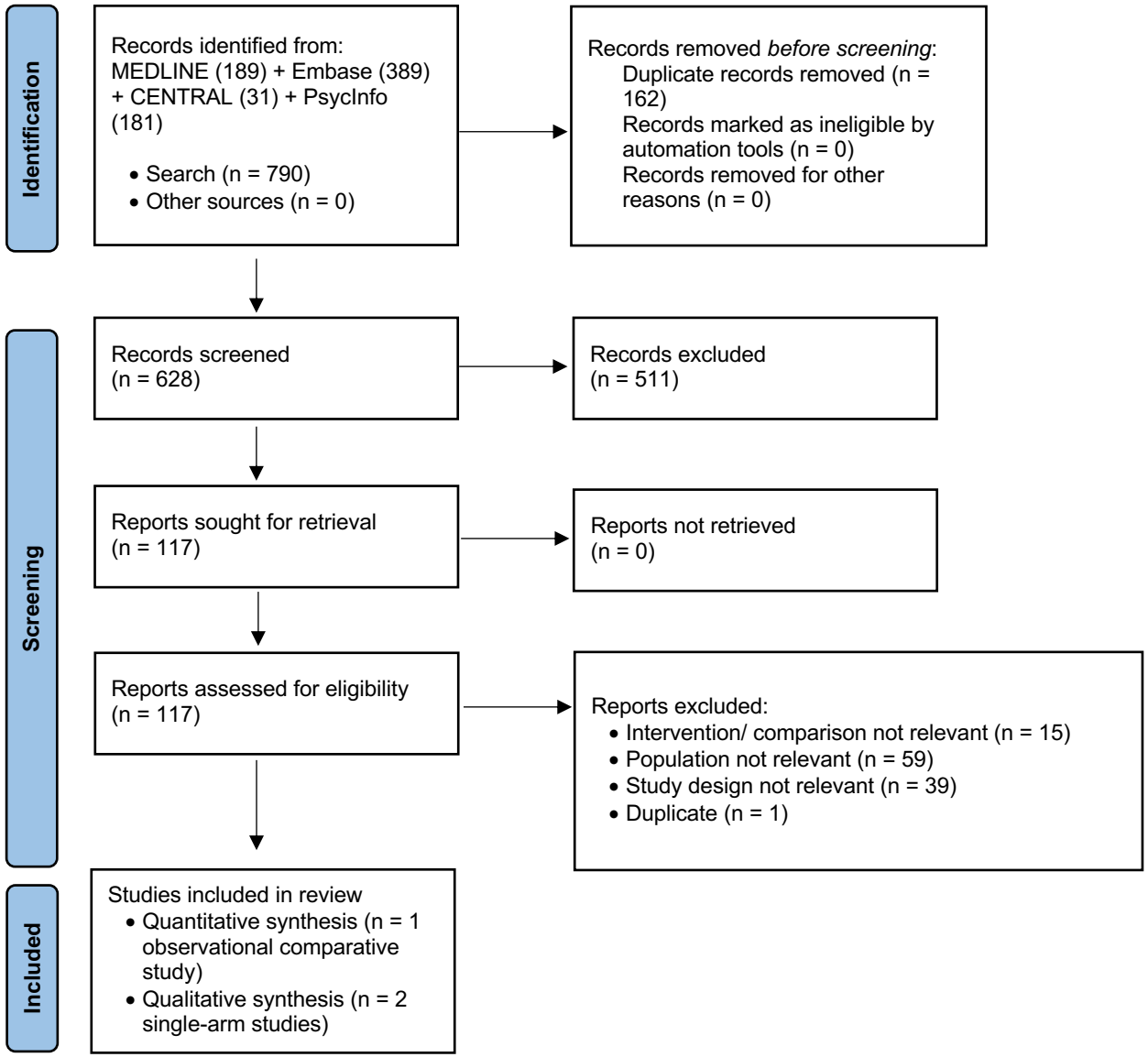
42. exp animals/ not humans/

43. 41 not 42

44. (comment or historical article or news).pt.

45. 43 not 44

Appendix 2. PRISMA flowchart



Appendix 3. Excluded studies

Refid	Bibliography	Reason for exclusion
3	Schonhofer, Bernd, Geiseler, Jens, Dellweg, Dominic, Fuchs, Hans, Moerer, Onnen, Weber-Carstens, Steffen, Westhoff, Michael, Windisch, Wolfram 2021. Prolonged Weaning: S2k Guideline Published by the German Respiratory Society Respiration, 99(11): 982-1083.	Study design not relevant
12	Samsel, Chase 2020. 22.2 DELIRIUM IN PALLIATIVE CARE Journal of the American Academy of Child and Adolescent Psychiatry, 59(10 Supplement): S34.	Population not relevant
18	Prommer, Eric 2020. Midazolam: an essential palliative care drug Palliative Care & Social Practice, #volume#(#issue#): 1-12.	Study design not relevant
26	Maeda, Sayaka, Kato, Itaru, Umeda, Katsutsugu, Hiramatsu, Hidefumi, Takita, Junko, Adachi, Souichi, Tsuneto, Satoru 2020. Continuous deep sedation at the end of life in children with cancer: experience at a single center in Japan Pediatric hematology and oncology, 37(5): 365-374.	Study design not relevant
35	Jacobowski, Natalie, Truba, Natalie, Radbill, Linda-Maritza 2020. Beyond the SSRI: Assessment and Treatment of Depression and Anxiety in Pediatric Palliative Care (SA506) Journal of Pain and Symptom Management, 59(2): 494-495.	Study design not relevant
37	Haug, Shelly, Dye, Alicia, Durrani, Sara 2020. End-of-Life Care for Neonates: Assessing and Addressing Pain and Distressing Symptoms Frontiers in pediatrics, 8(#issue#): 574180.	Study design not relevant
40	Gangopadhyay, Maalobeeka, Kearney, Julia A. 2020. PEDIATRIC DELIRIUM IN SPECIAL POPULATIONS: EXPANDING THE ROADMAP Journal of the American Academy of Child and Adolescent Psychiatry, 59(10 Supplement): S33.	Study design not relevant
46	Cortezzo, DonnaMaria E., Meyer, Mark 2020. Neonatal End-of-Life Symptom Management Frontiers in pediatrics, 8(#issue#): 574121.	Study design not relevant
47	Bhakta, Hemangini, Jacobowski, Natalie, Bass, Alice 2020. Creation of a Delirium Bundle: A Pediatric Palliative Care Team QI Project to Standardize Delirium Management Pediatrics, 146(1): 221.	Study design not relevant
58	Ripamonti, Carla Ida, Toffolatti, Luisa 2019. OPTIMAL END OF LIFE CARE Breast, 48(Supplement 2): S22-S23.	Population not relevant
59	Okhuysen-Cawley, Regina, Lasa, Javier, Casas, Jessica, Mahoney, Daniel, Namrata, Walia, Santucci, Gina, Carpenter, Alana, Roy, Kevin, Coleman, Ryan, Brown, Kyle, Krennerich, Emily, Bastero, Patricia, Erkonen, Gwen, Achuff, Barbara-Jo, Jain, Parag, Tume, Sebastian, Pinto, Venessa, Thammasitboon, Satid, Virk, Manpreet, Crozier, Faith 2019. Analgesia and sedation for compassionate extubation: A review of the medical literature Critical Care Medicine, 47(1 Supplement 1): #Pages#.	Study design not relevant
68	Moazam, Cherine, Hirst, Jeremy, Mesarwi, Paula, Atayee, Rabia S. 2019. Ketamine: When Delirium and Desperation Call for a Hero Journal of pain & palliative care pharmacotherapy, 33(3-4): 120-124.	Population not relevant
69	Mharapara, Primrose 2019. Mental illness in hemodialysis: An urban outpatient unit approach...2019 Canadian Association of Nephrology Nurses and Technicians Annual Conference, 24-26 October 2019, Edmonton, Alberta CANNT Journal, 29(2): 16-17.	Population not relevant
73	Lichtenstein, Ann H., Jolliffe, Anna B., Ameli, Rezvan 2019. Psychiatric symptom management in adult and pediatric cancer patients: Anxiety, delirium, and depression Handbook of supportive oncology and palliative care: Whole-person adult and pediatric care., #volume#(#issue#): 131-149.	Intervention/ comparison not relevant

75	Kucukdag, Meltem, Yektas, Cigdem 2019. Hyperactive delirium and its symptomatic treatment with risperidone in a paediatric patient: a case report Psychiatry and Clinical Psychopharmacology, 29(2): 223-225.	Population not relevant
84	Fortney, Christine A. 2019. Palliative and End-of-Life Care for Infants and Their Families in the NICU: Building a Program of Research Journal of Pediatric Nursing, 49(#issue#): 104-105.	Intervention/ comparison not relevant
90	Berger, Ann M., Hinds, Pamela S., Puchalski, Christina M. 2019. Handbook of supportive oncology and palliative care: Whole-person adult and pediatric care Handbook of supportive oncology and palliative care: Whole-person adult and pediatric care., #volume#(#issue#): #Pages#.	Intervention/ comparison not relevant
91	Bendle, Lizzie, Laddie, Joanna 2019. Symptomatic palliative care for children with neurodisability Paediatrics and Child Health (United Kingdom), 29(10): 431-435.	Study design not relevant
94	Tatterton, Michael J. 2018. Anticipatory prescribing and advance care planning in palliative care for children and young people Nurse Prescribing, 16(5): 228-233.	Study design not relevant
96	Singh, Arun L., Barone, Silvana, Hutton, Nancy 2018. A brave new world: Terminal weaning of mechanical ventilation outside of the ICU in a pediatric patient Pediatrics, 142(1): #Pages#.	Study design not relevant
97	Siegel, Mari, Bigelow, Suzanne 2018. Palliative Care Symptom Management in The Emergency Department: The ABC's of Symptom Management for The Emergency Physician The Journal of emergency medicine, 54(1): 25-32.	Population not relevant
99	Schildmann, Eva, Pornbacher, Sebastian, Kalies, Helen, Bausewein, Claudia 2018. 'Palliative sedation'? A retrospective cohort study on the use and labelling of continuously administered sedatives on a palliative care unit Palliative medicine, 32(7): 1189-1197.	Population not relevant
102	Okhuysen-Cawley, R. 2018. A structured approach to refractory pain and other distressing symptoms in critically-ill children Pediatric Critical Care Medicine, 19(6 Supplement 1): 168.	Population not relevant
106	Maeda, Sayaka, Kato, Itaru, Umeda, Katsutsugu, Hiramatsu, Hidefumi, Takita, Junko, Adachi, Souichi, Tsuneto, Satoru 2018. Continuous deep sedation at the end of life in children with cancer Pediatric Blood and Cancer, 65(Supplement 3): S104.	Duplicate
112	Jacobowski, Natalie, Buxton, David, Casas, Jessica 2018. From the pre-verbal infant to the non-verbal adult: Increasing your delirium recognition and treatment skill set in challenging pediatric and adult patients Journal of Pain and Symptom Management, 55(2): 566-567.	Study design not relevant
113	Jacob, Jean, Matharu, Jaskirt K., Palat, Gayatri, Sinha, Sudha, Brun, Eva, Wiebe, Thomas, Segerlantz, Mikael 2018. End-of-Life Treatments in Pediatric Patients at a Government Tertiary Cancer Center in India Journal of palliative medicine, 21(7): 907-912.	Intervention/ comparison not relevant
114	Hussain, Sara, Al Jarman, Khulood, Hussain, Sahar 2018. Sleeping beauty syndrome presenting with insomnia BMJ Case Reports, 2018(#issue#): 1-3.	Population not relevant
116	Hauer, Julie, Clark, Catherine, Jarek, Holly 2018. Anticipating death in children and adults with childhood onset severe central nervous system impairment: A case series review Journal of Pain and Symptom Management, 55(2): 631.	Intervention/ comparison not relevant
120	Fay, Zara, O'Boyle, Colm 2018. An Exploration of How Specialist Palliative Care Nurses Identify and Manage Patients with Existential Distress Journal of Pain and Symptom Management, 56(6): e69.	Population not relevant

123	Cortina, G., Klingkowski, U., Ojinaga, V., Neu, N., Giner, T. 2018. Safety of levomepromazine for the treatment of refractory agitation in critically ill children Pediatric Critical Care Medicine, 19(6 Supplement 1): 194-195.	Population not relevant
124	Chong, Lee Ai, Chong, Poh Heng, Chee, Joyce 2018. Pharmacological Management of Symptoms in Children with Life-Limiting Conditions at the End of Life in the Asia Pacific Journal of palliative medicine, 21(9): 1242-1248.	Study design not relevant
132	Andersen, Lezlie H., Thorvilson, Megan J., Schiltz, Brenda M., Collura, Christopher A. 2018. The role of pediatric palliative care in congenital Zika syndrome Pediatrics, 142(1): #Pages#.	Population not relevant
133	Aidoo, Ella, Rajapakse, Dilini 2018. End of life care for infants, children and young people with life-limiting conditions: planning and management: the NICE guideline 2016 Archives of disease in childhood. Education and practice edition, 103(6): 296-299.	Study design not relevant
140	Trowbridge, Amy, Stewart, Miriam T., Rhee, Eileen, Hwang, Jennifer M. 2017. Providing Palliative Care in Rare Pediatric Diseases: A Case Series of Three Children with Congenital Disorder of Glycosylation Journal of Palliative Medicine, 20(1): 104-106.	Study design not relevant
162	Burns, Jamie, Jackson, Kevin, Sheehy, Kathy A., Finkel, Julia C., Quezado, Zenaide M. 2017. The Use of Dexmedetomidine in Pediatric Palliative Care: A Preliminary Study Journal of palliative medicine, 20(7): 779-783.	Intervention/ comparison not relevant
167	Ziplow, Jason, Chadha, Tanya, Wen, Andy 2016. Psychosis, seizures, and autonomic instability in a teenage girl with an ovarian mass Critical Care Medicine, 44(12 Supplement 1): 534.	Population not relevant
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177	Pillai, Sekhar C., Brilot, Fabienne, Mohammad, Shekeeb S., Hong, Martin, Dale, Russell C., Jones, Hannah, Sharpe, Cynthia, Nosadini, Margherita 2016. Symptomatic treatment of children with anti-NMDAR encephalitis Developmental Medicine and Child Neurology, 58(4): 376-384.	Population not relevant
182	Pao, Maryland 2016. Pediatric psychopharmacology: To use or not to use at the end of life Psycho-Oncology, 25(SUPPL. 2): 5.	Study design not relevant
189	Lam, Y. W. Francis, Lam, Ansom, Macy, Brad 2016. Pharmacokinetics of Phenobarbital in Microenema Via Macy Catheter Versus Suppository Journal of pain and symptom management, 51(6): 994-1001.	Population not relevant
192	Jacobowski, Natalie 2016. Pediatric palliative care and child and adolescent psychiatry Journal of the American Academy of Child and Adolescent Psychiatry, 55(10 Supplement 1): S303.	Population not relevant
197	Evin, Adrien, Libot, Jerome, Denis, Nathalie 2016. Relevance of using intranasal midazolam in palliative care: About a literature review Palliative Medicine, 30(6): NP257-NP258.	Study design not relevant
198	Drolet, Caroline, Roy, Helene, Laflamme, Julie, Marcotte, Marie-Eve 2016. Feasibility of a Comfort Care Protocol Using Oral Transmucosal Medication Delivery in a Palliative Neonatal Population Journal of palliative medicine, 19(4): 442-50.	Intervention/ comparison not relevant

202	Davies, Nathan, Mathew, Rammya, Wilcock, Jane, Manthorpe, Jill, Sampson, Elizabeth L., Lamahewa, Kethakie, Iliffe, Steve 2016. A co-design process developing heuristics for practitioners providing end of life care for people with dementia BMC palliative care, 15(#issue#): 68.	Population not relevant
205	Dahlin, Constance, Coyne, Patrick J., Ferrell, Betty R. 2016. Advanced practice palliative nursing Advanced practice palliative nursing., #volume#(#issue#): #Pages#.	Intervention/ comparison not relevant
208	Blankenburg, M. 2016. Symptom control in life-threatening neuropadiatric disorders Neuropediatrics, 47(Supplement 1): #Pages#.	Population not relevant
218	Wuerz, Timothy, Shrestha, Rajeet, Appleby, Brian S. 2015. Rapidly Progressive Young-Onset Dementias: Neuropsychiatric Aspects Psychiatric Clinics of North America, 38(2): 221-232.	Population not relevant
219	Torres, A. 2015. Aspartylglucosaminuria (AGU) in Spain. A rare form of progressive mental retardation Journal of Intellectual Disability Research, 59(SUPPL. 1): 21.	Population not relevant
220	Thiels, C., Kohler, C., Stahl, A., Lucke, T., Saft, C. 2015. Therapeutic options in treatment of juvenile huntington disease: Difference to adult patients Neuropediatrics, 46(Supplement 1): #Pages#.	Population not relevant
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Appendix 4. Risk of bias assessment

Observational comparative studies (ROBINS-I)

Study details	Bias*	Authors' judgements	Support for judgement
Peled 2020 **Retrospective cohort study**	**Bias due to confounding**	Critical	This study was not randomised and did not report results adjusted for confounding factors when comparing groups.
	Bias in selection of participants into the study	Critical	This study was not randomised nor participants or providers randomly selected. The choice of drug was at the discretion of the treating psychiatrist. No adjustment techniques were used to attempt to correct for the presence of selection biases.
	Bias in classification of interventions	-	
	Bias due to deviations from intended interventions	-	
	Bias due to missing data	-	
	Bias in measurement of outcomes	-	
	Bias in selection of the reported result	-	
	Overall bias	**Critical**	

* The Cochrane Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) was used to assess the risk of bias in observational studies. When we considered the bias due to confounding and selection bias to be "serious" or "critical", the overall risk of bias for the study was also considered "serious" or "critical" and other domains were not assessed (triage method).

Appendix 5. Summary of results from observational non-comparative studies

Study details	Methods	Participants	Interventions	Outcomes measured in the study	Summary of results
Ref ID 309 **Hohl, 2013** **Canada** **Clinical trial registration: not reported** **Funding:** **Small grant from Manitoba Institute of Child Health** **Conflict of interest: none** **Contact details: chohl@wrha.mb.ca**	Study design: retrospective chart review Setting: 2 Hospitals in Canada Study dates: November 2006 - July 2011	Children aged 16 days to 17 years treated with methotrimeprazine in the last 2 weeks of life N = 18 Age: 8 days to 17 years Sex: not reported Wide range of health conditions: malignancy, trauma, neurodegenerative diseases, congenital diseases	Methotrimeprazine, various doses, concentrations timings and routes, all delivered in hospital. *In several instances, multiple medications were administered to palliate a single symptom	• Methotrimeprazine efficacy • Adverse events	• Methotrimeprazine appears to be an efficacious medication for treating agitation at the end of life (note: effectiveness of methotrimeprazine was rarely recorded in detail, and often several drugs were given to palliative the same symptom.) • No abnormal neuromuscular movements, dystonic reactions, or signs of NMS were documented • Sedation was the most common side effect (n = 6)
Ref ID 335 **Van Der Zwaan 2011** **Netherlands** **Clinical trial registration: not reported** **Funding: none declared** **Conflict of interest: non declared** **Contact details: schieveld@mumc.nl**	Study design: Case series Setting: Paediatric Intensive Care Unit Study dates: not reported	Critically ill children with refractory agitation N = 4 Mean age 8.4 years, range 0.7-15 years Sex: 3 males, 1 female Health condition: ilocytic astrocytoma, postoperative tracheostomy closure, respiratory insufficiency due to swollen tongue, respiratory insufficiency	Methortimeprazine, 1mg-10mg, 2-4 times per day, IV or enterally in hospital	• Reduction of refractory agitation and restoration of comfort in all patients • Adverse events	• Reduced refractory agitation and restoration of the comfort of the child and everyone involved. • two patients developed delirium for which an individually titrated dosage of haloperidol remained insufficient or ineffective • a third patient suffered from therapy-resistant agitation during slowly weaning from sedation

	due to pulmonary hypertension	• The last patient experienced repeated periods of agitation due to progressive pulmonary hypertension

Appendix 6. Indirect evidence

Guidelines and other non-primary sources

Study ID	Methods	Population	Intervention(s)	Main conclusions/ recommendations	References	Notes (optional)
Ref 37 **Haug, 2020** **United States**	Review article Methods not stated	Neonates receiving end of life care	Pharmacological interventions	• Use benzodiazepines, opioids and consider barbiturates		P5 and table 1
Ref 46 **Cortezzo, 2020** **United states**	Review article Methods not stated	Neonates receiving end of life care	Pharmacological and non-pharmacological interventions	• Doses for demedetomidine, gabapentin, benzodiazepines and morphine included for agitation (not referenced)		P7, table 1
Ref 59 **Okhuysen-Cawley, 2018** **United States**	Review article MEDLINE® search from 1990 - 2018	Babies and children undergoing compassionate extubation	Pharmacological interventions and team communication	• Proactive rather than reactive use of sedation • Benzodiazepines, and consider carefully titrated propofol and ketamine if a high symptom burden is expected • Use of checklists; team huddles; and order sets may facilitate a smooth CE.		
Ref 91 **Bendle, 2019** **United Kingdom**	Review article Methods not stated	Children with neurodisabilities requiring palliative care	Pharmacological and non-pharmacological interventions	• Target potential triggers. • Non-pharm – environmental and		P433

				complimentary therapies • Pharm – neuropathic and antipsychotic agents, benzodiazepines and sedatives.		
Ref 94 **Tatterton, 2018** **United Kingdom**	Review article Methods not stated	Children with life limiting conditions	Pharmacological and non-pharmacological interventions	• Pharmacological – benzodiazepines and neuroleptics. • Non-pharmacological – distraction; physical contact; environment; music and complimentary therapy.		P231, box 4
Ref 133 **Aidoo, 2018** **United Kingdom**	Review article Methods not stated	Infants, children and young people with life limiting conditions	Pharmacological and non-pharmacological interventions	• Identify triggers. • Non-pharmacological – environment; reassurance; physical contact. • Pharmacological – benozodiazepines and neuroleptics.		P297, Box 3
Ref 229 **Rasmussen, 2015** **Canada**	Review article Methods not stated	Children with neurological conditions receiving palliative care	Pharmacological and non-pharmacological interventions	• Identify and treat triggers. • Non-pharmacological – environment; comfort; complimentary therapies. • Pharmacological – neuropathic agents; alpha-2-adrenergic receptor agonists;	• Cummings MR, Pharmacologic management of behavioral instability in medically ill pediatric patients. 2004. • Wusthoff CJ, Management of common neurologic symptoms in pediatric palliative care:	P160-1

				benzodiazepines; antipsychotics; sedatives.	Seizures, agitation, and spasticity. 2007. • Hauer J, Gabapentin successfully manages chronic unexplained irritability in children with severe neurologic impairment. 2007. • Hauer J. Improving comfort in children with severe neurological impairment. 2012. • Siden HB, Physician variability in treating pain and irritability of unknown origin in children with severe neurological impairment. 2013.
Ref 335 **Mosher, 2021** **United Kingdom**	Book chapter No methods stated	Children receiving palliative care	Pharmacological and non-pharmacological	Non-pharmacological: • Environmental; comfort; orientation. Pharmacological: • Haloperidol; risperidone; benzodiazepines.	
Ref 418 **Klick, 2010** **United States**	Review article Methods not stated	Children receiving palliative care	Pharmacological interventions	• Benzodiazepines and neuropathic agents	

Ref 466 **Wusthoff, 2007** **United Kingdom**	Review article, Methods not stated	Children receiving palliative care	Pharmacological and non-pharmacological interventions	• Identify triggers. • Non-pharmacological – environment; touch; voice. • Pharmacological – Benzodiazepines; neuroleptics; adrenergic agonists and antagonists; barbiturates and sedatives	P717-726, tables 4-6

Indirect evidence from primary studies

Study ID	Methods	Population	Intervention(s)	Main study results
Ref 124 **Chong 2018** **Malaysia (However looks at 18 countries across Asian Pacific)** **Sep 2015 – Feb 2016**	Survey	Survey of Asia Pacific Hospice Palliative Care Network	Looking at drugs available to respondents	• 9.3% of respondents had no drugs to manage restlessness. • In those who did have available drugs, benzodiazepines and antipsychotics were most commonly used. • 24% said if drugs could not be given orally or by injection there was no available treatment for restlessness. In those that did have options available, buccal and intranasal midazolam, and rectal diazepam were the most common.