Cochrane Response

APPM guidelines Q3. Gastrointestinal Failure in children with Severe Neurological Impairment

October 2021

Authors:

Tim Warlow, Gemma Villanueva, Jill Yates, Naomi Taylor, Pat Sartori, Bindu Koodiyedath, Anna-Karenia Anderson

Trusted evidence.
Informed decisions.
Better health.

Table of Contents

Summary

This systematic review was performed as part of an APPM guideline on "Gastrointestinal Failure in children with Severe Neurological Impairment"

Review question

What pharmacological and non-pharmacological interventions are effective for the management of symptoms resulting from gastrointestinal failure in infants, children and young people with palliative care needs?

Selection criteria

See Methodology report for the full systematic review protocol.

Population

CYP with severe neurological impairment and gastrointestinal failure who may benefit from a palliative care approach.

For this guideline, we define gastrointestinal failure in line with the emerging British Society of Paediatric Gastroenterology Hepatology and Nutrition definition of Gastrointestinal Dystonia:

'Clinical manifestations of distress (pain behaviour, hypertonicity, retching, vomiting, autonomic phenomenon, abdominal distension) attributable to the gastro-intestinal tract, as diagnosed by a specialist multidisciplinary nutrition team, directly and indirectly related to feeding and bowel habit, where confounding systems distress have been addressed or excluded.'

These children do not adhere to the traditional definitions of gastrointestinal failure which include the following:

1) Reduction of functional gastrointestinal mass below that needed for digestion and absorption of fluid and nutrients for maintenance in adults and growth in children.[1]
2) A child requiring greater than 50% of calories by parenteral route for greater than or equal to 28 days post term corrected gestational age.[2]

However, due to their symptoms and distress and neuro-gastrointestinal dysfunction, they are unable to tolerate feed, leading to nutritional insufficiency and in many cases ultimately failure of enteral nutrition.

Intervention

- Pharmacological
- Non-pharmacological

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.

We identified relevant systematic reviews, reviews and guideline and the references of the included studies were checked for relevance. In addition, the guideline group collected indirect evidence and existing guidance. This includes studies that did not meet inclusion criteria for our primary search, review and primary studies from gastroenterology, surgery, neurology, palliative care relating to this group of children. Also included are findings from Delphi studies, national and international consensus meetings where sources are acclaimed national organisations made up of experts in their field.

Methods

Search methods

MEDLINE (Ovid) and Embase (Ovid), Cochrane CENTRAL (Wiley) and PsycINFO (OVID) 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 assessment, we used the Cochrane 'Risk of Bias' tool for RCTs (Higgins 2011).

Summarising and interpreting results

We planned on using the GRADE approach to interpret findings and create 'Summary of findings' tables following the GRADE handbook (Schünemann 2019); however, no studies were identified for inclusion.

Search results

We retrieved a total of 1538 records. After deduplication, 1399 unique abstracts were screened. We retrieved the full text of 53 records and after screening excluded 52 records. No RCTs or observational comparative studies were identified for inclusion. However, we identified a case report.

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

Included studies

No RCTs or observational comparative studies were identified for inclusion. However, we identified a case report.

Main results

Pharmacological interventions

No RCTs or comparative studies were found. However, we identified a case report. See Appendix 4 for a summary of the main results.

Non-pharmacological interventions

No studies were identified.

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 5.

References

Included studies

Not applicable

Observational non-comparative studies

Wahid 2017

- Wahid AM, Powell CV, Davies IH, Evans JA, Jenkins HR. Intestinal failure in children and young people with neurodisabling conditions. Archives of disease in childhood. 2017 May 1;102(5):475-6.

Indirect evidence

- Coad J, Toft A, Lapwood S, et al. Blended foods for tube-fed children: a safe and realistic option? A rapid review of the evidence". Arch Dis Child 2017;102:274–278
- J Hauer. Feeding intolerance in Children with Severe Impairment of the Central Nervous System. Children. 2017 Dec;5:1-11
- Broekaert et al. The use of jejunal tube feeding in children: A position paper by the Gastroenterology and Nutrition Committees of the ESPGHAN 2019. JPGN 2019 Aug;69:2
- Richards C. A. Does retching matter? Reviewing the evidence – Physiology and forces. Journal of Paediatric Surgery. 2019;54:750-759
- Romano et al. European Society for Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for the Evaluation and Treatment of Gastrointestinal and Nutritional Complications in Children With Neurological Impairment. JPGN 2017;65:2.
- S Mordekar, M Velayundhan, D Campbell. Feed-induced dystonias in children with severe central nervous system disorders. JPGN. 2017 Sept;65:3.
- Antao et al. Effectiveness of alimemazine in controlling retching after Nissen fundoplication. Journal of Paediatric Surgery. 2005;40;1737-1740.
- Merhar et al. A retrospective review of cyproheptadine for feeding intolerance in children less than three years of age: effects and side effects. Acta Paediatrica. 2016 May;105:967-970
- Collins A, Mannion R, Broderick A, et al. Gabapentin for the treatment of pain manifestations in children with severe neurological impairment: a single-centre retrospective review. BMJ Paediatrics Open 2019;3:e000467.
- Hauer JM, Wical BS, Charnas L. Gabapentin Successfully Manages Chronic Unexplained Irritability in Children With Severe Neurologic Impairment. Paedaitrics 2007;119e519
- Hauer JM, Solodiuk JC. Gabapentin for Management of Recurrent Pain in 22 Nonverbal Children with Severe Neurological Impairment: A Retrospective Analysis. Journal of Palliative Medicine. 2015;18:5

- Manini ML, Camilleri M, Grothe R, Lorenzo CD. Application of Pyridostigmine in paediatric gastrointestinal motility disorders: A case series. Paediatr Drugs. 2018 Apr;20(2):173-180

Other references

1. Barclay AR, Paxton CE, Gillett P, et al. Regionally acquired intestinal failure data suggest an underestimate in national service requirements. Archives of Disease in Childhood 2009;94:938-943
2. Barclay AR, et al., The continued rise of paediatric home parenteral nutrition use: Implications for service and the improvement of longitudinal data collection, Clinical Nutrition (2014), http://dx.doi.org/10.1016/j.clnu.2014.11.009
3. 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.
4. 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

Acknowledgments

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

Appendix 1. Search strategy

MEDLINE (Ovid) Search Strategy

(Revised April 29, 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. exp Intestinal Obstruction/

35. exp Constipation/

36. (ileus or constipat*).mp.

37. ((gut or gastrointestin* or gastro-intestin*or intestin* or bowel or colon* or duoden* or jejun* or ileum or ileal) adj3 (obstruct* or fail* or dysmotilit*)).mp.

38. 34 or 35 or 36 or 37

39. 9 and 33 and 38

40. 33 and 38

41. limit 40 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)")

42. 39 or 41

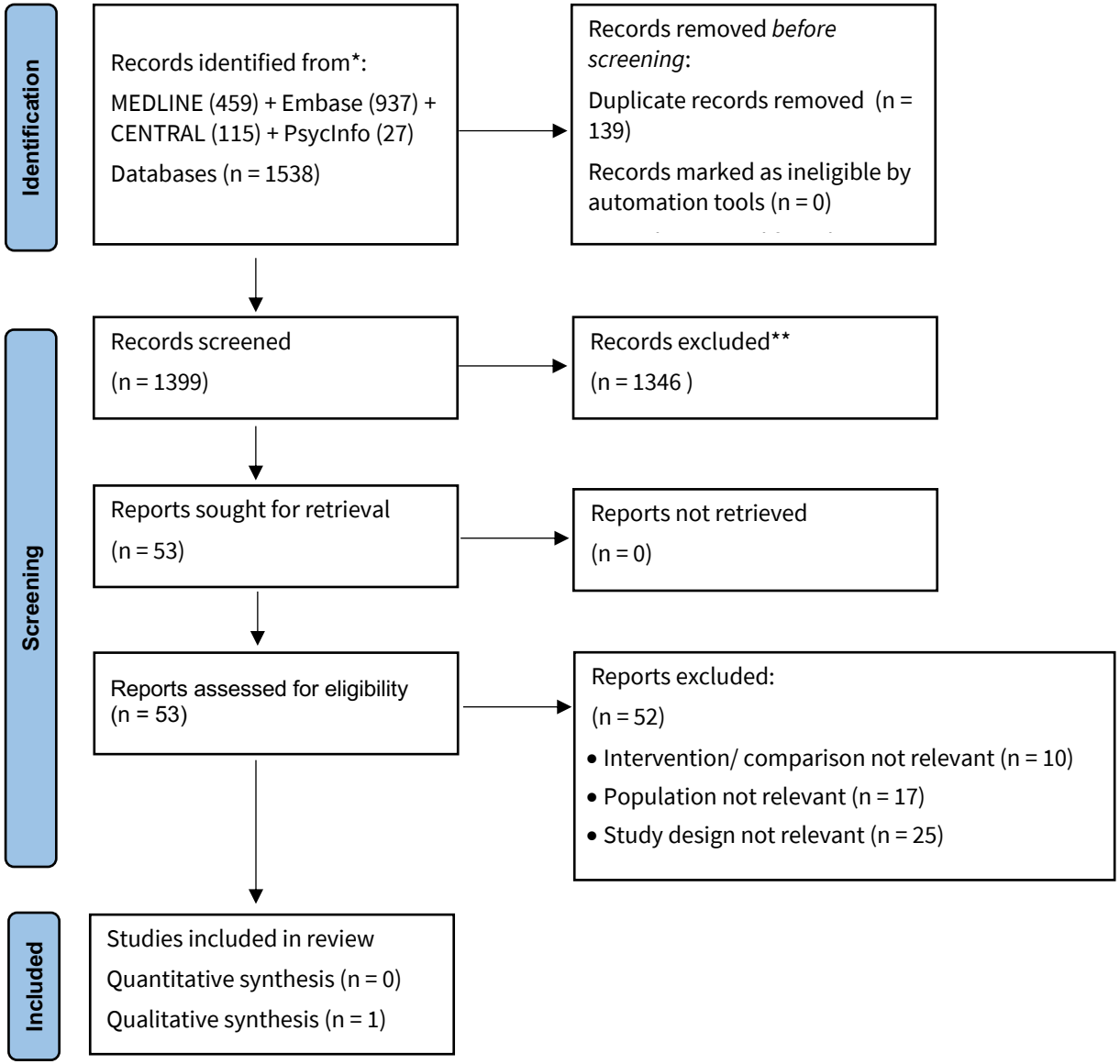
43. exp animals/ not humans/

44. 42 not 43

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

46. 44 not 45

Appendix 2. PRISMA flowchart



Appendix 3. Excluded studies

Refid	Bibliography	Reason for exclusion
2	2010. Other complementary therapies Focus on alternative and complementary therapies, 15(2): 175.	Study design not relevant
30	Agarwal T, Aboumarzouk O. Shariff U. Antakia R. Nelson R. L. 2010. Cisapride for intestinal constipation Colorectal disease, 12(#issue#): 38.	Population not relevant
55	Almeida, P. S., Penna, F. J. 2000. Chronic intestinal Pseudo-obstruction in childhood International Pediatrics, 15(2): 79-86.	Intervention/ comparison not relevant
62	Amin, Seema, Dickerman, Mindy, Miller, Elissa, Levy, Carly 2021. Transdermal buprenorphine in children with complex chronicconditions: A case series Pediatrics, 147(3): 550.	Population not relevant
67	Anonymous 1980. Constipation Nursing, #volume#(17): 751-5.	Study design not relevant
82	Athavale, Akshay, Athavale, Tegan, Roberts, Darren M. 2020. Antiemetic drugs: What to prescribe and when Australian Prescriber, 43(2): 49-56.	Population not relevant
116	Bauters, T., Robays, H., Van De Velde, V., Verlooy, J., Van Neck, A., Laureys, G., Benoit, Y. 2013. Restrospective analysis on the use of laxatives in children in palliative care Pediatric Blood and Cancer, 60(SUPPL. 3): 42.	Intervention/ comparison not relevant
119	Beardsmore, S., Fitzmaurice, N. 2002. Palliative care in paediatric oncology European Journal of Cancer, 38(14): 1900-1907.	Population not relevant
123	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
125	Bennett, M. B. 1973. Care of the dying South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 47(34): 1558-60.	Study design not relevant
128	Benze, G., Geyer, A., Alt-Epping, B., Nauck, F. 2012. [Treatment of nausea and vomiting with 5HT3 receptor antagonists, steroids, antihistamines, anticholinergics, somatostatinantagonists, benzodiazepines and cannabinoids in palliative care patients : a systematic review] Behandlung von ubelkeit und erbrechen mit 5HT3-antagonisten, steroiden, antihistaminika, anticholinergika, somatostatinanaloga, benzodiazepinen und cannabinoiden bei palliativpatienten : ein systematisches review., 26(5): 481-99.	Study design not relevant
152	Bonertz, Lori, Dyck, Nancy, Kantz, Valerie 2007. Provision of methadone infusion by a community pharmacy for a pediatric patient requiring palliative care Canadian Pharmacists Journal, 140(5): 298.	Population not relevant
177	Brown, Sarah, Davies, Natalie, Heather, Nicky, Cole, Caroline, Smyth, Enda, Batra, Akshay, Beattie, R. M. 2017. Long term outcome of intestinal rehabilitation in children over a period of 15 years-a single centre experience Journal of Pediatric Gastroenterology and Nutrition, 64(Supplement 1): 858-859.	Intervention/ comparison not relevant
190	Cairns, P. A. 2020. Decision-making in neonatal intestinal failure:palliative or active care? Archives of Disease in Childhood, 105(SUPPL 1): A117.	Population not relevant

192	Cameron, Jean-Christy F., Vaillancourt, Regis, Major-Cook, Nathalie, Boland, Margaret, Zucker, Marc, Lariviere, Doris 2013. Clinical recovery of chronic intestinal pseudo-obstruction with cisapride in a complex pediatric patient The American journal of hospice & palliative care, 30(4): 403-5.	Intervention/ comparison not relevant
195	Candy, Bridget, Jones, Louise, Vickerstaff, Victoria, Larkin, Philip J., Stone, Patrick 2018. Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care The Cochrane database of systematic reviews, 6(#issue#): CD006332.	Study design not relevant
236	Cheung, H. M., Lam, H. S., Tam, Y. H., Lee, K. H., Ng, P. C. 2009. Rescue treatment of infants with intestinal failure and parenteral nutrition-associated cholestasis (PNAC) using a parenteral fish-oil-based lipid Clinical Nutrition, 28(2): 209-212.	Population not relevant
254	Coad, Jane, Toft, Alex, Lapwood, Susie, Manning, Joseph, Hunter, Mark, Jenkins, Huw, Sadlier, Clare, Hammonds, Julie, Kennedy, Ailsa, Murch, Simon, Widdas, David 2017. Blended foods for tube-fed children: a safe and realistic option? A rapid review of the evidence Archives of disease in childhood, 102(3): 274-278.	Study design not relevant
256	Cockington, R. A., Vining, R. A. 1985. Prescribing for children. Part II. Symptomatic treatment Current Therapeutics, 26(11): 57-80.	Study design not relevant
305	Di Nardo, Giovanni 2019. New therapeutic options in children with chronic intestinal pseudo-obstruction Italian Journal of Pediatrics, 45(Supplement 3): #Pages#.	Study design not relevant
333	Duval, M., Wood, C. 2002. [Treatment of non-painful symptoms in terminally ill children] Traitement des symptomes non douloureux chez l'enfant en fin de vie., 9(11): 1173-8.	Study design not relevant
380	Feudtner, Chris, Freedman, Jason, Kang, Tammy, Womer, James W., Dai, Dingwei, Faerber, Jennifer 2014. Comparative effectiveness of senna to prevent problematic constipation in pediatric oncology patients receiving opioids: A multicenter study of clinically detailed administrative data Journal of Pain and Symptom Management, 48(2): 272-280.	Population not relevant
386	Flerlage, Jamie E., Baker, Justin N. 2015. Methylnaltrexone for Opioid-Induced Constipation in Children and Adolescents and Young Adults with Progressive Incurable Cancer at the End of Life Journal of palliative medicine, 18(7): 631-3.	Population not relevant
402	Friedrichsdorf, Stefan J., Foster-Barber, Audrey, Hauer, Julie, Tremonti, Nadia, Ullrich, Christina K. 2010. Advanced management of distressing non-pain symptoms in pediatric palliative care Journal of Pain and Symptom Management, 39(2): 328-329.	Intervention/ comparison not relevant
461	Goulet, Olivier, Ruemmele, Frank 2006. Causes and management of intestinal failure in children Gastroenterology, 130(2 Suppl 1): S16-28.	Population not relevant
468	Greenfield, Katie, Holley, Simone, Schoth, Daniel E., Harrop, Emily, Howard, Richard F., Bayliss, Julie, Brook, Lynda, Jassal, Satbir S., Johnson, Margaret, Wong, Ian, Liossi, Christina 2020. A mixed-methods systematic review and meta-analysis of barriers and facilitators to paediatric symptom management at end of life Palliative Medicine, 34(6): 689-707.	Study design not relevant
496	Hauer, Julie 2017. Feeding Intolerance in Children with Severe Impairment of the Central Nervous System: Strategies for Treatment and Prevention Children (Basel, Switzerland), 5(1): #Pages#.	Study design not relevant
514	Herrick, A. L. 1996. Advances in palliative care for the patient with scleroderma Current opinion in rheumatology, 8(6): 555-60.	Study design not relevant
532	Hotta, R., Natarajan, D., Thapar, N., Hotta, Ryo, Natarajan, Dipa, Thapar, Nikhil 2009. Potential of cell therapy to treat pediatric motility disorders Seminars in Pediatric Surgery, 18(4): 263-273.	Intervention/ comparison not relevant

583	Johnson, Liza-Marie, Spraker, Holly L., Coleman, Jamie L., Baker, Justin N. 2012. An unusual case of Ogilvie syndrome in a pediatric oncology patient receiving palliative care after failed treatment with neostigmine Journal of palliative medicine, 15(9): 1042-6.	Population not relevant
586	Jordan-Ely, Julie, Dobson, Kyla M., Appaduray, Shaun, Hynson, Jenny, Kornberg, Andrew J., Hutson, John M., Southwell, Bridget R. 2015. Management of severe faecal impaction in an adolescent with Duchenne muscular dystrophy (DMD) receiving palliative care Journal of paediatrics and child health, 51(3): 351-2.	Population not relevant
716	Lee, Noel, Wald, Arnold 2011. The pharmacokinetics, pharmacodynamics, clinical efficacy, safety and tolerability of linaclotide Expert opinion on drug metabolism & toxicology, 7(5): 651-9.	Study design not relevant
856	Moss, Jonathan, Dickerson, David, Nunnally, Mark, Jacobsohn, Eric 2011. Methylnaltrexone treats opioid-induced bowel dysfunction in three critically ill patients American Journal of Gastroenterology, 106(SUPPL. 2): S369.	Study design not relevant
915	Noritz, G., Jersak, T., Tumin, D., Fosselman, D., Humphrey, G. L., Testa, M. 2019. Defining end stage gastrointestinal failure in patients with neurologic impairment Developmental Medicine and Child Neurology, 61(Supplement 3): 130.	Intervention/ comparison not relevant
917	Novak, Chris, Hogg, Amanda, Sue, Kyle, Davies, Dawn 2021. Peripherally acting mu-opioid receptor antagonists for treatment of opioid-induced constipation in children Paediatrics & child health, 26(2): e105-e109.	Population not relevant
966	Pawliuk, Colleen, Widger, Kim, Dewan, Tammie, Brander, Gina, Brown, Helen L., Hermansen, Anne-Mette, Gregoire, Marie-Claude, Steele, Rose, Siden, Harold Hal 2020. Scoping review of symptoms in children with rare, progressive, life-threatening disorders BMJ supportive & palliative care, 10(1): 91-104.	Study design not relevant
967	Peck, S. N., Altschuler, S. M. 1992. Pseudo-obstruction in children Gastroenterology nursing : the official journal of the Society of Gastroenterology Nurses and Associates, 14(4): 184-8.	Study design not relevant
980	Pettit, Kevin A., Beardmore, Daniel 2020. Constipation and asymmetric rectal tone in a 10-month-old girl Pediatrics in Review, 41(#issue#): S79-S81.	Population not relevant
996	Portnoi, M. V., Tsarev, N. I. 1969. [Elongated sigmoid colon] Udlinennaia sigmovidnaia kishka., 102(1): 46-50.	Population not relevant
1053	Roy, A., Simon, G. B. 1987. Intestinal obstruction as a cause of death in the mentally handicapped Journal of mental deficiency research, 31 (Pt 2)(#issue#): 193-7.	Intervention/ comparison not relevant
1072	Samuels, L. A. 2009. Pharmacotherapy update: hyoscine butylbromide in the treatment of abdominal spasms Clinical Medicine: Therapeutics, #volume#(1): 647-655.	Study design not relevant
1077	Santucci, Gina, Mack, Jennifer W. 2007. Common gastrointestinal symptoms in pediatric palliative care: nausea, vomiting, constipation, anorexia, cachexia Pediatric clinics of North America, 54(5): 673-x.	Study design not relevant
1093	Schuffler, M. D., Rohrmann, C. A., Chaffee, R. G., Brand, D. L., Delaney, J. H., Young, J. H. 1981. Chronic intestinal pseudo-obstruction. A report of 27 cases and review of the literature Medicine, 60(3): 173-96.	Study design not relevant
1107	Sewell, Mathew D., Eastwood, Deborah M., Wimalasundera, Neil 2014. Managing common symptoms of cerebral palsy in children BMJ (Online), 349(#issue#): g5474.	Intervention/ comparison not relevant

1116	Shaw, Tressia M. 2012. Pediatric palliative pain and symptom management Pediatric Annals, 41(8): 329-334.	Intervention/ comparison not relevant
1200	Tabbers, Merit M., Boluyt, Nicole, Berger, Marjolein Y., Benninga, Marc A. 2011. Nonpharmacologic Treatments for Childhood Constipation: Systematic Review Pediatrics, 128(4): 753-761.	Study design not relevant
1231	Thapar, N., Burns, A. 2012. Use of enteric nervous stem cells to treat motility disorders: Ready for prime time? Neurogastroenterology and Motility, 24(SUPPL.2): 15.	Study design not relevant
1241	Torres, Clarivet, Dussan, Monica, Sandler, Anthony, Zavosky, Patricia, Parvathi, Mohan 2009. A new intestinal care program (ICP) at children's national medical center: Another year of experience Pediatric Transplantation, 13(SUPPL. 1): 47.	Study design not relevant
1263	Uzcategui Arauz A, Arias Guzman Y. Jaen D. 1995. Chronic constipation. Use of cisapride Estrenimiento cronico. Uso del cisapride, 49(3): 218.	Population not relevant
1322	Westfal, Maggie L., Goldstein, Allan M. 2017. Pediatric enteric neuropathies: diagnosis and current management Current Opinion in Pediatrics, 29(3): 347-353.	Study design not relevant
1331	Wiseman, L. R., Faulds, D. 1994. Cisapride. An updated review of its pharmacology and therapeutic efficacy as a prokinetic agent in gastrointestinal motility disorders Drugs, 47(1): 116-52.	Study design not relevant
1332	Wiskin, A. E., Cullen, M., Pidgeon, C., Beattie, R. M., Cole, C., Owens, D. R., Burge, D. M. 2011. Home parenteral nutrition in children: 10 year experience from a single centre Proceedings of the Nutrition Society, 70(OCE5): E289.	Population not relevant

Appendix 4. Summary of results from observational non-comparative studies

Study details	Methods	Participants	Interventions	Outcomes measured in the study	Main conclusions
Ref ID 1290 **Wahid 2017** **UK** **Clinical trial registration: not reported** **Funding: not reported** **Conflict of interest: not reported**	Study design: case report Setting: hospital Study dates: not reported	13-year-old boy with life limiting condition. Cerebral Palsy (CP) epilepsy, severe learning difficulties and autistic features Palliative child with intestinal failure	Central venous catheter (CVC) and total parenteral nutrition (PN) Nasogastric (NG) feeds were not tolerated and nasojejunal (NJ) feeding was also unsuccessful	• Methotrimeprazine efficacy • Adverse events	• TPN was provided post operatively and continued for 5 months. During this period child did not tolerate NJ feeds. • Severe gut dysmotility was confirmed throughout the remaining gut. Slow introduction of comfort feeds via NG and mouth. This gradually improved as child started to tolerate

Contact details: **amarwahid@ doctors.** **org. uk**	more volume and reached full enteral feeds by 3 months. • TPN may be indicated for a period of gastrointestinal rest prior to reintroduction of feeds in children with gastrointestinal failure.

Appendix 5. Indirect evidence

Guidelines and other non-primary sources

Study ID	Methods	Population	Intervention(s)	Main conclusions/ recommendations	References	Notes (optional)
Review 1. **"Blended foods for tube-fed children: a safe and realistic option? A rapid review of the evidence"** **Coad et al 2016** **United Kingdom** **August – December 2014.**	Rapid review of literature using systematic principals. PubMed, Medline, Cinahl, PsychINFO, Google Scholar.	Children and adults using blended diet as alternative feed.	Blended diet to replace commercial formula for feeds.	• Blended diets come with risks of inadequate fluid, protein, calorie density, contamination. • For those with high calorie needs it is recommended a high calorie formula be added to blended diet. • Effectiveness of blended diet should be monitored with input/output recording, weight monitoring and symptom change. • Significant social benefit of blended diet and parent satisfaction. • Reports tolerance of greater feed volume, reduction in pain, reflux and constipation with its use. • Blended diet via gastrostomy might be effective for improving food intake for those with chronic diarrhoea and post fundoplication surgery.	• Novak P, Wilson KE, Ausderau K, et al. The use of blenderized tube feedings. Infant Child Adolesc Nutr 2009;1:21–3. • Schuitema CFJ. Basics in clinical nutrition: diets for enteral nutrition home-made diets. J Clin Nutr Metab 2009;4:e168–9.	Population primarily related to but not limited to children with severe neurological impairment.
Review 2. **"Feeding intolerance in Children with Severe Impairment of the Central Nervous System."** **Hauer J** **2017** **United States**	Literature review and narrative guideline.	CYP with severe neurological impairment and feed intolerance.	Multiple	Multiple including: • Importance of accurate fluid and calorie assessment in CYP with SNI. • Importance of exploration of other sources of pain including GORD and constipation. • Importance of home care plans for parents to follow to manage symptoms. • Importance of advance care planning. • Consider 30% reduction in feed volume with monitoring of weight and symptoms to assess benefit 2-4 weeks.	• Hauer, J.; Houtrow, A.J.; Section on Hospice and Palliative Medicine, Council on Children with Disabilities. • Pain Assessment and Treatment in Children with Significant Impairment of the Central Nervous System. Pediatrics 2017, 139, • Langen, T.; Ciarla, C.; Zangen, S.; Di Lorenzo, C.; Flores, A.F.; Cocjin, J.; Reddy, S.N.; Rowhani, A.; Schwankovsky,	

- Bolus feeds should be <15ml/kg/feed, continuous rate <8ml/kg/hr.
- Alteration of feed volume, rate, calories and gastrostomy tube venting to reduce GI distension. (1)
- Gabapentin pregabalin and tricyclic antidepressant trial for visceral hyperalgesia and central pain. (2)
- Clonidine for pain perception during gastric and colonic distention. (3)
- Cyproheptadine to improve feed tolerance, decrease emesis and retching post fundoplication. (4)
- Presence of persistent peripheral oedema is a poor prognostic factor.

L.; Hyman, P.E. Gastrointestinal motility and sensory abnormalities may contribute to food refusal in medically fragile toddlers. J. Pediatr. Gastroenterol. Nutr. 2003, 37, 287–293

- 2. Lee, K.J.; Kim, J.H.; Cho, S.W. Gabapentin reduces rectal mechanosensitivity and increases rectal compliance in patients with diarrhoea-predominant irritable bowel syndrome. Aliment. Pharmacol. Ther. 2005, 22, 981–988.]
- Hauer, J.; Solodiuk, J. Gabapentin for Management of Recurrent Pain in 22 Nonverbal Children with Severe Neurological Impairment: A Retrospective Analysis. J. Palliat. Med. 2015, 18, 453–456.
- Hauer, J.; Wical, B.; Charnas, L. Gabapentin successfully manages chronic unexplained irritability in children with severe neurologic impairment. Pediatrics 2007, 119, e519–e522
- 3. Kuiken, S.D.; Tytgat, G.N.; Boeckxstaens, G.E. Review article: Drugs interfering with visceral sensitivity for the treatment of functional gastrointestinal disorders—

					The clinical evidence. Aliment. Pharmacol. Ther. 2005, 21, 633–651. • 4. Rodriguez, L.; Diaz, J.; Nurko, S. Safety and efficacy of cyproheptadine for treating dyspeptic symptoms in children. J. Pediatr. 2013, 163, 261–267. • Merhar, S.L.; Pentiuk, S.P.; Mukkada, V.A.; Meinzen-Derr, J.; Kaul, A.; Butler, D.R. A retrospective review of cyproheptadine for feeding intolerance in children less than three years of age: Effects and side effects. Acta Paediatr. 2016, 105, 967–970.	
Review 3: **"The use of jejunal tube feeding in children: A position paper by the Gastroenterology and Nutrition Committees of the ESPGHAN 2019."** **Broekaert et al.** **2019** **Pan European** **Literature review until 2018.**	Systematic literature review and consensus meeting. Literature review Medline 1980-2015. PubMed and Cochrane. Evidence categorised according to GRADE. Consensus vote on recommendations.	Patients for whom Jejunostomy tube feeding is a consideration.	Jejeunostomy tube insertion and management.	• Symptoms of nausea vomiting, gagging retching and feed intolerance should be assessed by an appropriate multidisciplinary team including addressing anatomical and non-gastrointestinal factors prior to placement of JT. • Decision to place jejunostomy tube should be multidisciplinary. • A trial of continuous gastric feeding with hydrolysed or elemental formula should be given prior to JTF. • Consider a trial of at least 1 prokinetic drug to promote oral or gastric feeding before instituting jejunal feeding. • Jejeunal feeding is the route of choice for providing enteral nutrition in children with failure of oral or intragastric feeds or gastric outlet obstruction.		Further recommendations related to surgical approach and care of jejeunal tube itself not included in this extraction. Please see original paper for these aspects. Summary of evidence on prokinetic agents - little evidence - fewer adverse events with erythromycin as

				• A trial of JTF should be considered in children with paediatric intestinal pseudo-obstruction who fail gastrostomy feeding. • In children with severe neurological impairment JTF should be considered as an alternative to fundoplication and gastrostomy feeding where the child has severe GORD with risk of aspiration. • Gastric decompression and aspiration should be used in children being jejeunally fed with high risk of GORD and pulmonary aspiration due to accumulation of gastric residue and abnormal distention (this is likely in GID due to foregut dysmotility and retrograde travel of jejeunal condense leading to symptomatic gastric distention).		compared to metoclopramide - risk of tardive dyskinesia with metoclopramide
Review 4: **"Does retching matter? Reviewing the evidence – Physiology and forces."** **Richards C. A.** **2019** **United Kingdom**	Literature review and narrative review of evidence.	CYP with SNI post antireflux surgery.	Management of retching and vomiting in post reflux surgery patients.	• 'Wrap failure' is more common in children with SNI than the 'neurologically normal' child as diaphragmatic stressors (retching, seizures, chronic resp disease) are more common. Retching is a cause not a symptom of wrap herniation. • Retching may not be due to GORD as it is a reflex triggered by the vomiting centre in the brainstem and it is associated with the symptom of nausea. • Causes of retching and vomiting should be considered other than problems with GIT anatomy post surgery: duodenal stenosis, superior mesenteric artery syndrome, mucosal disease (e.g. eosinophilic oesophagitis) – hydrocephalus, shunt dysfunction, raised ICP, electrolyte	• Fried MD, Khoshoo V, Secker DJ, et al. Decrease in gastric emptying time and episodes of regurgitation in children with spastic quadriplegia fed a whey-based formula. J Pediatr 1992;120:569–72. • Minor G, Ochoa JB, Storm H, et al. Formula switch leads to enteral feeding tolerance improvements in children with developmental delays. Glob Pediatr Health 2016;3: • Cook RC, Blinman TA. Alleviation of retching and feeding intolerance after fundoplication. Nutr Clin Pract 2014;29:386–96. • Cook RC, Blinman T. The case of the wretched retcher. Infant	

disturbance, constipation. Metabolic disturbances

- Chronic respiratory disease and cough worsen vomiting, consider Azithromycin prophylaxis focussed on improving respiratory symptoms may improve vomiting. Treat underlying dystonia as this often improves vomiting.
- To reduce afferent visceral hypersensitivity:

Trial of whey based feed leading to improved gastric emptying (1)

Predigested formula trial (2)

Avoid hyperosmolar feeds (3)

Consider blenderised feeds.(4)

Avoid overfeeding and calorie excess (5)

Smaller more frequent boluses (6)

Continuous gastric feeds

Consider jejeunal feeding +/- gastric drainage (7)

- Consider prokinetic (Domperidone and metoclopramide) trial (8)
- Consider trial of alimemazine. (9)
- Consider trial of Cyproheptadine (10)
- Considrer trial of Seratonin 5HT3 antagonist (11)
- Consider Levomepromazine.
- Consider trial of Neurokinin receptor antagonist (12).

Child Adolesc Nutr 2009;1:94–7.

- Godbole P, Margabanthu G, Crabbe DC, et al. Limitations and uses of gastrojejunal feeding tubes. Arch Dis Child 2002;86:134–7
- Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastorenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 2018;66:516–54.
- Godbole P, Margabanthu G, Crabbe DC, et al. Limitations and uses of gastrojejunal feeding tubes. Arch Dis Child 2002;86:134–7.
- Raval MV, Philips JD. Optimal enteral feeding in children with gastric dysfunction: surgical jjunostomy vs image-guided gastrojejunal tube placement. J Pediatr Surg 2006;41:1679–82.
- Carachi R, Currie JM, Steven M. New tools in the treatment of motility disorders in

	• Reduce/ review polypharmacy especially when many drugs modify function of the GI tract. • Be cautious of patients selected for fundoplication – extreme caution in those with gut dysmotility or features of activation of the emetic reflex pre-operatively • In children with post op retching and wrap dislocation or herniation redo fundoplication risks worsening symptoms and repeated failure.	children. Semin Pediatr Surg 2009;18:274–7. • Antao B, Ooi K, Ade-Ajayi N, et al. Effectiveness of alimemazine in controlling retching after Nissen fundoplication. J Pediatr Surg 2005;40:1737–40. • Rodriguez L, Diaz J, Nurko S. Safety and efficacy of cyproheptadine for treating dyspeptic symptoms in children. J Pediatr 2013;163:261– • Richards CA, Andrews PLR. Emesis as a model system for the study of functional bowel disease. J Pediatr Gastroenterol Nutr 2007;45:S120–6 • Hauer J. Feeding intolerance in children with severe impairment of the central nervous system: strategies for treatment and prevention. Children 2018;5:1. • Chong K, Dhatariya K. A case of severe, refractory diabetic gastroparesis managed by prolonged use of aprepitant. Nat Rev Endocrinol 2009;5:285–8. • Fahler J, Wall GC, Leman BI. Gastroparesis-associated refractory nausea treated with

					aprepitant. Ann Pharmacother 2012;46:e38. • Cristofori F, Thapar N, Saliakellis E, et al. Efficacy of the neurokinin-1 receptor antagonist aprepitant in children with cyclical vomiting syndrome. Aliment Pharmacol Ther 2014;40:309–17.
Review 5 **"European Society for Paediatric Gastroenterology,** **Hepatology and Nutrition Guidelines for the Evaluation** **and Treatment of Gastrointestinal and Nutritional** **Complications in Children With Neurological Impairment"** **Romano et al. 2017** **Pan-european.**	Systematic literature review and consensus meeting. Literature review Medline 1980-2015. Consensus vote on recommendations.	CYP with neurological impairment. Children with Cerebral palsy referred to as major subgroup of for purpose of this document.	Management of nutrition and gastrointestinal problems in children with neurological impairment.	• ESPGHAN has clear recommendations for assessing nutritional status in children with SNI. This is vital to provide optimal nutrition and avoid overfeeding. • GORD: A trial of PPI with careful clinical follow up is acceptable alternative to invasive investigations where appropriate. • Use of upper GI endoscopy including biopsies, oesophgeal pH monitoring and intraluminal impedance monitoring should be considered. pH monitoring esp to distinguish GORD from foregut dysmotility not related to GORD. Consider SMA syndrome in those with scoliosis and malnutrition. • Trials of feed thickener and whey based formulas should be considered. • PPIs should be first line treatment for GORD. • Use of prokinetics should be reserved for uncontrolled GORD due to weak efficacy and side effects. Regular re-evaluation of efficacy. • Constipation: Ensure adequate fibre and fluid intake. Treatment should follow NICE guidelines constipation in children. Initial treatment with disimpaction and osmotic maintenance agents. Macrogol and paraffin should be used in caution with those at high risk of aspiration. Enemas may be required to	

	support fecal disimpaction alongside osmotic agents. • General feeding issues: • Assessment of postural and orthopedic issues is important as they may contribute to feeding difficulties. • Whey based formula trial to be considered in those with delayed gastric emptying to improve retching, gagging and GORD. • Standard 1kcal/ml polymeric age-approprite formula is the appropriate first feed option in children with SNI. • For poor volume tolerance consider high energy density (1.5kcal/ml) formula containing fibre. • Human milk, standard infant formula or nutrient dense infant formula is indicated in infants with SNI. • Low calorie, high fibre and micronutrient replete formula for the maintenance of enteral tube feeding is recommended once nutritional rehabilitation is complete. • Blenderised diets can be used but to be used with caution due to concerns about nutritional adequacy and safety. • Enteral tube feeding should be started before the development of undernutrition. Gastrostomy is the preferred long term tube feeding method. • A combination of continuous nocturnal feeds and daytime bolus feeds should be considered in those with high caloric needs or with poor tolerance to volume.	

	• Jejeunal feeding should be used in cases of aspiration due to GORD, refractory vomiting, retching and bloating in children with SNI.

Indirect evidence from primary studies

Study ID	Methods	Population	Intervention(s)	Study results	Notes (optional)
Paper 1: **"Feed-induced dystonias in children with severe central nervous system disorders."** **S Mordekar, M Velayundhan, D Campbell.** **United Kingdom** **2012-2017**	Retrospective case series	CYP presenting with status dystonicus (and pain) with evidence of feed induced dystonic spasms. CYP with GORD associated Sandifer excluded.	Withholding feeds and use of TPN to manage symptoms. Octreotide intravenously (n=2 cases)	• Witholding feeds led to resolution of symptoms. • Restarting even 5ml/hr via gastric or jejeunal tube using extensively hydrolysed/elemental or electrolyte solution led to return of dystonia. • Patients with feeds withheld treated with TPN experienced resolution of symptoms.	12 children. Age 5m-15.8 years (mean 9.5yrs). All taking antidystonic medications. All had pH studies and gastroscopy and biopsy with no evidence of reflux or oesophagitis. 8 had fundoplication (confirmed to be intact at time of presentation).
Paper 2: **"Effectiveness of alimemazine in controlling retching after Nissen fundoplication"** **Antao et al.** **United Kingdom** **December 2002-2003.**	Prospective double blind randomised crossover placebo-controlled study. Exclusion criteria: hepatic or renal impairment, hypothyroidism	CYP neurological impairment. Post Nissen fundoplication for GORD. All gastrostomy fed.	1 week alimemazine, 1 week placebo with crossover. Alimemazine 0.25mg/kg TDS (max 2.5mg per dose).	• Mean number of retching episodes with alimemazine significantly reduced compared with placebo. • No adverse effects of Alimemazine reported. One subject discontinued due to drowsiness. • Concluded Alimemazine safe and effective for retching post nissen fundoplication.	• Recommended dosing 0.25mg/kg TDS. • Phenothiazine H1 receptor antagonist acting at vomiting centre. Antispasmodic smooth muscle effect. • 15 subjects, 12 enrolled with completed diaries. Age 8-180months (median 36)
Paper 3:	Retrospective chart review of under 3s seen in neonatal	39 children under 3yrs.	Cyproheptidine starting dose 0.23mg/kg/d mean	• SFX – in 25.6% mild sleepiness (10.2%),	• Recommended dosing 0.5-1mg/kg/day in three

"A retrospective review of cyproheptadine for feeding intolerance in children less than three years of age: effects and side effects." **Merhar et al.** **United States** **2011-2015**	follow up clinic prescribed cyproheptadine for feed intolerance (fullness or discomfort with feeds, retching and/or abdominal distention or vomiting) Exclusion: Those prescribed cyproheptadine for appetite stimulation.	Post NICU patients (18 with prematurity ((46%) 29 with brain injury (74%). 59% had gastrostomy feeding (or 61% tube fed to include all artificial feeding), 230.5% had nissen fundoplication. All except 1 had been tried on H2RA and PPIs. Most remained on an 'acid blocker'	TDS (range 0.07-0.83mg/kg/d)	constipation (7.7%), behavioural tantrums increasing (5.1% - discontinued medication). SFX Sleepiness and constipation resolved with dose reduction. • Statistically significant weight increase (but no control group) • 66.7% symptom resolution. 28.2% some improvement in symptoms, 84.6% improved vomiting.	divided doses for patients <1yr. 1-2mg/kg/day in three divided doses for patients in older children. • Likely mechanism of effect: 5HT2A and 2B antagonist increasing gastric compliance. Antihistamine sedative effects. (Also anticholinergic activity)
Paper 4: **"Gabapentin for the treatment of pain manifestations in children with severe neurological impairment: a single centre retrospective review"** **Collins et al.** **Ireland** **2019**	Single centre retrospective chart review.	CYP attending joint gastroenterology and palliative care services with gastrointestinal cause of pain and distress. 42 patients 3m-63m age.	Gabapentin for central pain and visceral hyperalgesia. Pregabalin as second line option if gabapentin response inadequate or SFX.	• Response to Gabapentin good or very good overall in 60% patients. Worse in 2%. 71% noted improvement in irritability. 40% noted improvement in pain (reduced analgesia requirement) (55% no improvement, 5 undocumented). • SFX: None in 74%, reducing effectiveness in 10% (taking 60mg/kg/d), lethargy in 7% cases, alopecia, twitching, vomiting, raised LFTs also reported. • Discontinued in 36% with 80% of these switched to pregabalin. On pregabalin 25% good or very good	Not clear what criteria used for good or very good effect apart from notes report. No objective measures used. Also included patients with irritability of unknown origin as well as those with gastrointestinal symptoms. Pregabalin doses not reported.

				effect, 67% minimal or no effect.	
Paper 5 **"Gabapentin Successfully Manages Chronic Unexplained Irritability in Children With Severe Neurologic Impairment"** **Hauer JM, Wical BS, Charnas L.** **2006** **United states** **2006**	Retrospective single centre case series (n=9). 6/9 gastrostomy tube fed, 7th scheduled for gastrostomy.	CYP with SNI and irritability. Population had feed intolerance and irritability associated with feeds, defecation and flatus. Suspected due to visceral hypersensitivity.	Gabapentin	• 9 CYP. All cases had UGI endoscopy series (5/9 UGI endoscopy), several had PH studys with no significant pathology. All tried PPI with no improvement. 8/9 on successful constipation management. • Marked improvement with gabapentin trial. 5mg/kg/dose NOCTE increased every 3-7 days final doses 15-35mg/kg/day in three divided doses. Improved irritability, crying, feed tolerance, sleep, improved responsiveness. • 1 child discontinued due to nystagmus despite excellent symptom control. SFX mild sleepiness in some cases, transient only.	Age 9 months – 22yrs 1 child who was discontinued had good response to amitriptyline. No objective data to measure 'marked improvement'
Paper 6 **"Gabapentin for Management of Recurrent Pain in 22 Nonverbal Children with Severe Neurological Impairment: A Retrospective Analysis"** **Hauer JM, Solodiuk JC.** **2015**	Single Centre Retrospective study case note review (n=22) – notes and clinical records.	CYP with SNI in long term paediatric care facility with recurrent pain behaviours recorded on Individualised numeric rating scale (INRS). 64% had gastrointestinal symptoms.	Gabapentin 5-6mg/kg/day increased every 2-3 days to maximum 72mg/kg/d or until symptoms improved. (mean dose required 43mg/kg/day. All on medication for gastric acid suppression.	• Significant benefit (>50% reduction in frequency and severity) in recurrent pain behaviours in 21 patients (95%). • Some improvement in dystonia also noted. • Some had a decrease in vomiting, two who were	Criteria for benefit used was if two or more bedside nurses reported the patient to have greater than 50% benefit along with decrease in frequency and severity of episodes irritability. (Pain frequency determined by the use of PRN analgesics).

United States **2011-2014**				jejeunally fed were able to return to gastric feeding, weight gain noted in some.' • No significant side effects – mild transient sedation in a few.	Most patients on medications for seizures, spasticity and GORD. Mean age 11.4yrs (range not given but up to 27yrs).
Paper 7 **"Application of Pyridostigmine in paediatric gastrointestinal motility disorders: A case series."** **Manini ML, Camilleri M, Grothe R, Lorenzo CD.** **2017** **United States**	Retrospective case series	Heterogeneous population. Case series with one relevant case of child with SNI and feed intolerance 7yrs old.	Distention and poor motility despite laxatives. Pyridostigmine 10mg QDS (4mg/kg/day) started – reduced to 2mg/kg/day maintenance.	Significant improvement in bowels opening (from every 5 days to daily). Vomiting and abdominal distention improved. Feed tolerated at 50ml/hr over 20hrs daily. Weight gain continued. Stopping pyridostigmine lead to symptom recurrence.	