Bijlage Evidence tabellen en GRADE profielen

Evidence tabellen en GRADE profielen behorende bij de uitgangsvragen die via de GRADE methodiek zijn uitgewerkt.

Onderzoeksvraag 1: vocht- en voedingsinterventies

Vraag 1: Welke vocht- en voedingsinterventies zijn geschikt bij het symptomatisch behandelen van patiënten met misselijkheid en braken in de palliatieve fase?

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Uster A 2018	• Design: RCT • Funding: (1) grant provided by the Krebsliga Schweiz (Swiss Cancer Foundation, Switzerland), Number: KFS-2833-08-2011; (2) Werner und Hedy Berger-Janser Stiftung; CoI: none • Setting: single cancer centre, Switzerland • Sample size: N=58 • Duration: 6 months follow-up; recruitment 3/2012-10/2014	• Eligibility criteria: cancer patients with metastatic or locally advanced tumors of the gastrointestinal or the lung tracts; ECOG PS ≤2, life expectancy > 6 months • Exclusion criteria: (i) enteral tube feeding or parenteral nutrition, (ii) brain metastases or symptomatic bone metastases, (iii) ileus within the last month • *A priori* patient characteristics: ○ Mean age: 63.0y ○ M/F: 40/18 ○ Cancer type: colorectal 28%, NSCLC 28%, pancreas 26%	3-month nutrition and physical exercise program (N=29): • At least 3 nutritional counselling sessions • Use of nutritional goals and criteria • Group training sessions 2x60 min/week supervised by experienced physiotherapist: warm-up, strength and balance training exercises vs.	CRITICAL OUTCOMES • Nausea / vomiting: EORTC QLQ-C30 – symptom scale, change from baseline ○ At 3 months (N=43): 4.2 vs. 9.7 ○ At 6 months (N=38): 3.6 vs. 17.1, p<0.01 • Quality of life: EORTC QLQ-C30 – Global health status, change from baseline ○ At 3 months (N=43): 4.5 vs. 2.7 ○ At 6 months (N=38): 5.7 vs. 2.7, p=0.72 • Patient satisfaction: not reported • Adverse events: not reported	Level of evidence: high risk of bias • Randomly generated treatment allocations in sequentially numbered, sealed, opaque envelopes (block sizes of eight) • Treatment allocation was blinded from the primary investigator until completion of baseline assessment • No blinding of patients was used in group assignment. In addition, the provider of the physical exercise intervention and the dietician could not, by definition, be blinded

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
			Usual care (N=29)		• Blinding was used for data collection purposes only: a blinded physiotherapist assessed data on physical performance • Not all randomized patients were included in analysis

Abbreviations: CoI: conflict of interest; ECOG PS: Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0; NSCLC: non-small-cell lung cancer; RCT: randomised controlled trial.

References

Uster, A., et al., Effects of nutrition and physical exercise intervention in palliative cancer patients: A randomized controlled trial. Clinical Nutrition, 2018. 37(4): p. 1202-1209.

GRADE-tabel

Author(s): Usher

Question: A nutrition and exercise program compared to usual care for cancer patients with metastatic or locally advanced tumors of the gastrointestinal or the lung tracts

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a nutrition and exercise program	usual care	Relative (95% CI)	Absolute (95% CI)		
EORTC QLQ-C30 – nausea and vomiting symptom scale, change from baseline at 3 months												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	25	18	-	SMD **0.35 lower** (0.96 lower to 0.26 higher)	⨁◯◯◯ Very low[a,b,c]	CRUCIAAL
EORTC QLQ-C30 – nausea and vomiting symptom scale, change from baseline at 6 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a nutrition and exercise program	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious[b]	serious[c]	none	21	17	-	SMD **0.85 lower** (1.52 lower to 0.18 lower)	⨁◯◯◯ Very low[a,b,c]	CRUCIAAL

EORTC QLQ-C30 – global health status, change from baseline at 3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a nutrition and exercise program	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	serious[b]	serious[d]	none	25	18	-	SMD **0.1 higher** (0.5 lower to 0.71 higher)	⊕◯◯◯ Very low[a,b,d]	CRUCIAAL

EORTC QLQ-C30 – global health status, change from baseline at 6 months

1	randomised trials	serious[a]	not serious	serious[b]	serious[d]	none	21	17	-	SMD **0.17 higher** (0.47 lower to 0.81 higher)	⊕◯◯◯ Very low[a,b,d]	CRUCIAAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a nutrition and exercise program	usual care	Relative (95% CI)	Absolute (95% CI)		
Patient satisfaction - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL
Adverse events - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

CI: confidence interval; **SMD:** standardised mean difference

1.1.1.1 Explanations

a. Uster 2018: no blinding, no ITT analysis

b. No nausea at inclusion

c. CI around SMD includes -0.5

d. CI around SMD includes 0.5

Onderzoeksvraag 2: ondersteunende zorg

Vraag 2: welke ondersteunende zorg is geschikt bij het symptomatisch behandelen van misselijkheid en braken in de palliatieve fase?
Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Ernst 2009	• Design: systematic review • Funding: not reported; CoI: not reported • Search date: Nov 2008 • Databases: Medline, Embase, Cinahl, British Nursing Index, AMED, Cochrane Library • Study designs: RCTs • N included studies: N=14 RCTs	• Eligibility criteria: RCTs that evaluated the effectiveness of classical massage in a supportive palliative cancer care setting • Exclusion: reflexology, hand massage, shiatsu, acupressure, lymph drainage or other forms of non-classical massage	Massage therapy	-	• Unclear if selection and data extraction was done by independent researchers • No language restrictions • Quality appraisal with Jadad instrument • No relevant included RCTs
Kobayashi 2023	• Design: systematic review • Funding: JSPS KAKENHI (grant number 21H03236); CoI: none • Search date: July 2023 • Databases: PubMed, Cinahl, CENTRAL, Ichushi-Web of the Japan Medical Abstract Society databases	• Eligibility criteria: (i) patients with cancer over 18 years of age, (ii) intervention or observational studies that focused on relieving nausea and vomiting, (iii) nursing support, and (iv) quantitative data showing outcomes • Exclusion: papers clearly showing that nausea and vomiting were caused by cancer treatment, papers	Nursing support interventions	-	• Duplicate study selection and data extraction • Restricted to Japanese and English language • No quality appraisal of included studies • No relevant included RCTs

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Study designs: intervention or observational studies • N included studies: N=6 RCTs	in which over 20% of the participants did not have cancer, papers with secondary analyses			
Pan 2000	• Design: systematic review • Funding: in part by the Commonwealth Fund; CoI: see article • Search date: Sep 1998 • Databases: PubMed, CINAHL, CancerLit, AIDSLINE, Social Work Abstracts, PsycLit • Study designs: clinical reports or reviews • N included studies: N=11 RCTs	• Eligibility criteria: original clinical reports or reviews that evaluated the use of a CAM modality to treat pain, dyspnea, and nausea and vomiting in adult patients with incurable conditions who were near the end of life • Exclusion: patients with chronic conditions that were not fatal or not characteristic of most dying patients (degenerative joint diseases and arthritides, burns, chronic pain syndromes, post-operative pain, spinal cord, or other neurological injuries); were laboratory studies, case reports, anecdotes, surveys, or commentaries; or focused primarily on biological mechanisms, risk factors, predictors, prognosis, or central nervous system stimulation techniques	CAM modalities	-	• Duplicate study selection and data extraction • No language restriction • No quality appraisal of included studies • Relevant RCTs: no RCTs about nausea and vomiting

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Shin 2016	• Design: systematic review + meta-analysis • Funding: (1) KAMS Research Center, Korean Academy of Medical Sciences (KAMS), Korea, South; (2) The South Asian Cochrane Network and Centre, Christian Medical College, Vellore, India; CoI: none • Search date: Aug 2015 • Databases: Cochrane Central Register of Controlled Trials, Medline, Embase, Cinahl, PsycINFO, PubMed Cancer Subset, SADCCT, WHO ICTRP • Study designs: RCTs • N included studies: N=19 RCTs	• Eligibility criteria: RCTs evaluating massage with or without aromatherapy in adults and children diagnosed with cancer • Exclusion: touch therapies such as therapeutic touch, acupressure, and reflexology; inhalations and humidification methods	Massage with or without aromatherapy	-	• Duplicate study selection, data extraction and quality appraisal • No language restrictions • No relevant included RCTs
Thomas 2005	• Design: systematic review • Funding: Health Canada (#6795-15-2002/4780004); CoI: unclear • Search date: unclear • Databases: ERIC, Embase, Medline,	• Eligibility criteria: persons who are terminally ill, near death, or dying	Non-medical and non-surgical therapies	-	• Unclear if selection and data extraction was done by independent researchers • Unclear if language restrictions were used • No RCTs relevant to PICO

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Cinahl, AMED, PsycInfo, HealthStar, Sociological Abstracts, Cochrane Library • Study designs: RCTs and SR • N included studies: N=15 RCTs				
Towler 2013	• Design: systematic review of reviews • Funding: scholarship from the Cancer Experiences Collaborative, which was funded by the National Cancer Research Institute; CoI: none • Search date: 2000-2011 • Databases: Medline, Embase, AMED, Cinahl, Web of Science • Study designs: SR • N included studies: N=17 SR	• Eligibility criteria: reviews of the use of acupuncture for cancer supportive and palliative care • Exclusion: papers on acupressure, children and animals	Acupuncture	-	• Unclear if selection and data extraction was done by independent researchers • Limited to English studies • No relevant SR: all referenced RCTs are about CINV
Wu 2015	• Design: systematic review of reviews • Funding: Hospital Authority of Hong Kong (Reference number: 8110016609); CoI: none	• Eligibility criteria: SR that summarised clinical evidence on the effectiveness of acupuncture and related therapies for palliative care of cancer	Acupuncture and related therapies	-	• Duplicate study selection, data extraction and quality appraisal • Unclear if language restrictions were applied • No relevant SR: all referenced RCTs are

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Search date: July 2014 • Databases: Medline, Embase, Cochrane Database of Systematic Reviews, DARE, Chinese Biomedical Databases, Wan Fang Digital Journals and Taiwan Periodical Literature Databases • Study designs: SR • N included studies: N=23 SR				about CINV and/or in Chinese
Zeng 2018	• Design: systematic review • Funding: none; CoI: none • Search date: Jan 1999 – May 2016 • Databases: PubMed, CINAHL, PsycINFO, Embase • Study designs: controlled trials • N included studies: N=17 RCTs	• Eligibility criteria: studies that assessed the efficacy of a CAM therapy in a palliative or hospice setting • Exclusion: meeting abstracts and quasi-experimental studies	CAM modalities	-	• Duplicate study selection, data extraction and quality appraisal • Restriction to English literature • Jadad scale was used for quality appraisal • No relevant included RCTs

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Brøndum 2022	• Design: RCT • Funding: none; CoI: none • Setting: 3 hospices, Denmark • Sample size: N=136 • Duration: Jan 2015 – Oct 2019	• Eligibility criteria: terminally ill patients referred to one of the three hospices who experienced nausea or vomiting either at the time of admission or during their stay • Exclusion criteria: patients were excluded from the study if they had massive oedema in arms or legs, could not respond appropriately, or could not cooperate cognitively • *A priori* patient characteristics: ○ Age: <50y 3%, 50-60y 12%, 60-70y 38%, 70-80y 34%, >80y 13% ○ M/F: 37/75	Acupuncture daily for 3 days (N=68) vs. Usual care (N=68)	CRITICAL OUTCOMES • Nausea / vomiting: ○ Reduction of nausea score: 75% vs. 55%, p=0.028 ○ No nausea after intervention: 52% vs. 30% ○ No vomiting after intervention: 69% vs. 66%, p=0.725 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported	Level of evidence: high risk of bias • Allocation to the intervention or control group was performed by the nurse caring for the patient, randomly picking a sealed white envelope from a basket with completely identical envelopes • No blinding • No ITT analysis
Look 2021	• Design: RCT • Funding: none; CoI: none • Setting: single university centre, Malaysia • Sample size: N=40 • Duration: 9/2018-12/2018	• Eligibility criteria: adult palliative care patients aged 18 years and above and at least one symptom scoring ≥5/10 based on the ESAS • Exclusion criteria: patients who were confused based on the Confusion Assessment Method or non-communicative • *A priori* patient characteristics: ○ Mean age: 66.8 vs. 69.2y	Mindful breathing during 20' (N=20) vs. Standard care (N=20)	CRITICAL OUTCOMES • Nausea / vomiting: ○ Mean symptom reduction (ESAS) at end of intervention: mean rank 18.8 vs. 22.3, U=165.0, Z=-1.245, p=0.355 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported	Level of evidence: high risk of bias • Computer-generated random number list with separation of allocations into single sheets that were opened only on patient recruitment to allow allocation concealment • Open-label • ITT analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		○ M/F: 20/20 ○ Cancer type: gastrointestinal/hepatobiliary 40%, gynaecological 13%, breast 10%, urological 10%, lung 5% ○ Non-malignant disease: 15%			
Perkins 2022	• Design: RCT • Funding: Sue Ryder Leckhampton Court Hospice Research Department; CoI: none • Setting: 2 specialist palliative care units, UK • Sample size: N=57 • Duration: recruitment June 2010 – Jan 2018	• Eligibility criteria: diagnosis of advanced cancer with an estimated prognosis of less than 1 year but more than 3 days, nausea as at least moderate on a one/mild/moderate/severe scale OR had at least one vomit per day for the last 3 days, underlying cause for their nausea thought to be irreversible OR the patient has made an autonomous choice not to proceed with treatment for any potentially reversible cause, stable dose of corticosteroids if taking • Exclusion criteria: arm lymphoedema; weakness, fatigue or confusion sufficient that patient is unable to take part; previous history of acupuncture/acupressure for nausea or vomiting, or history of use of acupressure by a close	Active acupressure wristbands (N=28) vs. Placebo wristbands (N=27)	CRITICAL OUTCOMES • Nausea / vomiting: ○ Difference in average number of vomits: -0.7 vs. -0.8, p=0.9288 ○ Total number of as needed doses of antiemetics: 65 vs. 50, p=0.1317 ○ Escalation of antiemetics: 14/84 vs. 13/75 study days, p=0.957 ○ Nausea VAS: median 22.5 vs. 21, p=0.5736 ○ Time (hours) nauseated over last 24h: p=0.769 ▪ <1/4: 42/84 vs. 31/75 study days ▪ 1/4-1/2: 15/84 vs. 17/75 ▪ 1/2-3/4: 11/84 vs. 10/75 ▪ 3/4-1: 8/84 vs. 9/75 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: N=15 vs. 13, p=0.299	Level of evidence: low risk of bias • Pairs of active or placebo acupressure wristbands had previously been placed in sequential numbered envelopes according to a sequence derived from randomization.com • The bands were placed on participants' wrists at the correct P6 points by a member of the research team not involved with clinical decision making for the patient • Patient was assessed by a clinician (blinded to the type of acupressure bands in place) • 2/57 patients excluded from analysis • Some analyses are done on the level of study days instead of patients

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		relative; history of parkinsonism or parkinsonism on examination (as metoclopramide included in treatment escalation schedule for patients with suspected gastric stasis); sharing a room with another patient taking part in the study; unable to read or comprehend the questionnaires or Visual Analogue Scale (VAS) • *A priori* patient characteristics: ○ Median age: 65.5y vs. 67.0y ○ M/F: 7/48 ○ Cancer type: upper GI N=10, lower GI N=7, pancreas / gall bladder N=10, lung N=10, ovary N=8			

Abbreviations: 95%CI: 95% confidence interval; CAM: complementary and alternative medicine; CINV: chemotherapy-induced nausea and vomiting; CoI: conflict of interest; ECOG PS: Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0; ESAS: Edmonton Symptom Assessment System; ITT: intention-to-treat; NSCLC: non-small-cell lung cancer; OR: odds ratio; QOL: quality of life; RCT: randomised controlled trial; SR: systematic review; VAS: visual analogue scale; WHOQOL-BREF: World Health Organization quality of life questionnaire.

References

Arving C, Sjödén PO, Bergh J, Hellbom M, Johansson B, Glimelius B, Brandberg Y: Individual psychosocial support for breast cancer patients: a randomized study of nurse versus psychologist interventions and standard care. Cancer Nurs. 2007, 30:E10-9.

Billhult A, Bergbom I, Stener-Victorin E (2007) Massage relieves nausea in women with breast cancer who are undergoing chemotherapy. J Altern Complement Med 13(1):53–57.

Brondum, L., B. Markfoged, and J. Finderup, Acupuncture as a tool to reduce nausea in terminally ill patients. Scandinavian Journal of Caring Sciences, 2022. 36(4): p. 1046-1053.

Ernst, E., Massage therapy for cancer palliation and supportive care: a systematic review of randomised clinical trials. Supportive Care in Cancer, 2009. 17(4): p. 333-7.

Hunter, J.J.; Maunder, R.G.; Sui, D.; Esplen, M.J.; Chaoul, A.; Fisch, M.J.; Bassett, R.L.; Harden-Harrison, M.M.; Lagrone, L.; Wong, L.; et al. A randomized trial of nurse-administered behavioral interventions to manage anticipatory nausea and vomiting in chemotherapy. Cancer Med. 2020, 9, 1733–1740.

Kobayashi M et al. Nursing Support for Nausea and Vomiting in Patients With Cancer: A Scoping Review. Cureus 15(11): e48212. doi:10.7759/cureus.48212.

Lim JTW, Wong ET, Aung SKH. Is there a role for acupuncture in the symptom management of patients receiving palliative care for cancer? A pilot study of 20 patients comparing acupuncture with nurse-led supportive care. Acupunct Med 2011;29:173e179.

Look, M.L., et al., Symptom reduction in palliative care from single session mindful breathing: A randomised controlled trial. BMJ Supportive and Palliative Care, 2021. 11(4): p. 433-439.

Pan, C.X., et al., Complementary and alternative medicine in the management of pain, dyspnea, and nausea and vomiting near the end of life. A systematic review. Journal of Pain & Symptom Management, 2000. 20(5): p. 374-87.

Perkins, P., et al., Does acupressure help reduce nausea and vomiting in palliative care patients? A double blind randomised controlled trial. BMJ supportive & palliative care, 2022. 12(1): p. 58-63.

Sabet, P., et al., Effect of Spirituality-Based Palliative Care on Pain, Nausea, Vomiting, and the Quality of Life in Women with Colon Cancer: A Clinical Trial in Southern Iran. Journal of Religion & Health, 2023. 62(3): p. 1985-1997.

Shin, E.S., et al., Massage with or without aromatherapy for symptom relief in people with cancer. Cochrane Database of Systematic Reviews, 2016. 2016(6).

Thomas, R. and D. Wilson, Randomized controlled trials of non-medical and non-surgical therapies for palliative care: A literature review. Alternative Medicine Review, 2005. 10(3): p. 204-215.

Towler, P., A. Molassiotis, and S.G. Brearley, What is the evidence for the use of acupuncture as an intervention for symptom management in cancer supportive and palliative care: an integrative overview of reviews. Supportive Care in Cancer, 2013. 21(10): p. 2913-23.

Uster, A., et al., Effects of nutrition and physical exercise intervention in palliative cancer patients: A randomized controlled trial. Clinical Nutrition, 2018. 37(4): p. 1202-1209.

Wu, X., et al., Effectiveness of acupuncture and related therapies for palliative care of cancer: overview of systematic reviews. Scientific Reports, 2015. 5: p. 16776.

Zeng, Y.S., et al., Complementary and Alternative Medicine in Hospice and Palliative Care: A Systematic Review. Journal of Pain & Symptom Management, 2018. 56(5): p. 781-794.e4.

GRADE-tabellen

Auteur(s):

Vraagstelling: Acupressure wristbands versus placebo wristbands voor patients with terminal cancer and nausea

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	acupressure wristbands	placebo wristbands	Relatief (95% CI)	Absoluut (95% CI)		
Median difference in average number of vomits												
1	gerandomiseerde trials	niet ernstig	niet ernstig	niet ernstig	zeer ernstig[a]	niet gevonden	Median (IQR): -0.7 (-1.7 - 0) vs. -0.8 (-1.5 - -0.3)P=0.9288				⨁⨁◯◯ Laag[a]	CRUCIAAL
Total number of as needed doses of antiemetics												
1	gerandomiseerde trials	niet ernstig	niet ernstig	niet ernstig	zeer ernstig[b]	niet gevonden	65 vs. 50, p=0.1317				⨁⨁◯◯ Laag[b]	CRUCIAAL
Escalation of antiemetics (/ study days)												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	acupressure wristbands	placebo wristbands	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[c]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	14/84 (16.7%)	13/75 (17.3%)	**RR 0.96** (0.48 tot 1.91)	**7 minder per 1.000** (from 90 minder tot 158 meer)	⨁◯◯◯ Zeer laag[c,d]	CRUCIAAL
Median nausea VAS												
1	gerandomiseerde trials	niet ernstig	niet ernstig	niet ernstig	zeer ernstig[e]	niet gevonden	Median (IQR): 22.5 (6.5-58) vs. 21 (7-43) P=0.5736				⨁⨁◯◯ Laag[e]	CRUCIAAL
Time (hours) nauseated over last 24h (/ study day: < 1/4 hours)												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	acupressure wristbands	placebo wristbands	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[c]	niet ernstig	niet ernstig	ernstig[f]	niet gevonden	42/84 (50.0%)	31/75 (41.3%)	**RR 1.21** (0.86 tot 1.71)	**87 meer per 1.000** (from 58 minder tot 293 meer)	⨁⨁◯◯ Laag[c,f]	CRUCIAAL
Quality of life - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL
Patient satisfaction - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	acupressure wristbands	placebo wristbands	Relatief (95% CI)	Absoluut (95% CI)		
Adverse events (/ study days)												
1	gerandomiseerde trials	ernstig[c]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	15/84 (17.9%)	13/75 (17.3%)	**RR 1.03** (0.52 tot 2.02)	**5 meer per 1.000** (from 83 minder tot 177 meer)	⊕◯◯◯ Zeer laag[c,d]	CRUCIAAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

1.1.1.2 Explanations

a. Calculated OIS = 2493 (assuming MD of 0.1 and SD of 1.26) --> not reached

b. No information about CI, small sample size

c. Perkins 2022: outcome reported at the level of study days instead of patients

d. CI around RR includes 0.75 and 1.25

e. Calculated OIS = 10155 (assuming MD of 1.5 and SD of 38.15) --> not reached

f. CI around RR includes 1.25

Auteur(s):

Vraagstelling: Acupuncture versus usual care voor terminally ill patients with nausea or vomiting

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	**Studieopzet**	**Risk of bias**	**Inconsistentie**	**Indirect bewijs**	**Onnauwkeurigheid**	**Andere factoren**	**acupunctuure**	**usual care**	**Relatief (95% CI)**	**Absoluut (95% CI)**		
Proportion of patients with reduction in nausea score												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[b]	niet gevonden	39/52 (75.0%)	33/60 (55.0 %)	**RR 1.36** (1.03 tot 1.80)	**198 meer per 1.000** (from 17 meer tot 440 meer)	⨁⨁◯◯ Laag[a,b]	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	acupunctuur	usual care	Relatief (95% CI)	Absoluut (95% CI)		
Proportion of patients without nausea after intervention												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[b]	niet gevonden	27/52 (51.9%)	18/60 (30.0 %)	**RR 1.73** (1.09 tot 2.76)	**219 meer per 1.000** (from 27 meer tot 528 meer)	⨁⨁◯◯ Laag[a,b]	CRUCIAAL
Proportion of patients without vomiting after intervention												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	acupunctuur	usual care	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[b]	niet gevonden	33/52 (63.5%)	38/60 (63.3%)	**RR 1.00** (0.76 tot 1.33)	**0 minder per 1.000** (from 152 minder tot 209 meer)	⨁⨁◯◯ Laag[a,b]	CRUCIAAL
Quality of life - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL
Patient satisfaction - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	acupunctuure	usual care	Relatief (95% CI)	Absoluut (95% CI)		
Adverse events - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

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

1.1.1.3 Explanations

a. Brondum 2022: unclear allocation concealment, no blinding, 24/136 patients not included in analysis

b. CI around RR includes 1.25

Auteur(s):

Vraagstelling: Mindful breathing versus standard care voor palliative care patients with symptoms

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	mindful breathing	standard care	Relatief (95% CI)	Absoluut (95% CI)		
Mean symptom reduction at end of intervention												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[b]	niet gevonden	Mean rank 18.8 vs. 22.3, U=165.0, Z=-1.245, p=0.355				⨁◯◯◯ Zeer laag[a,b]	CRUCIAAL
Quality of life - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL
Patient satisfaction - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL
Adverse events - niet gerapporteerd												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	mindful breathing	standard care	Relatief (95% CI)	Absoluut (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

CI: Confidence interval

1.1.1.4 Explanations

a. Look 2021: no blinding

b. Insuffiicient data to calculate precision, small sample size

Onderzoeksvraag 3: medicamenteuze behandeling

Vraag 3: Wat is de beste keuze voor medicatie (metocloperamide vs domperidon, haloperidol, dexamethason, levomepromazine vs. olanzapine, serotonine-antagonisten, erythromycine, cyclizine, cannabis , gember) bij de behandeling van patiënten met misselijkheid en braken in de palliatieve fase?

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Cox 2015	• Design: systematic review • Funding: none; CoI: none • Search date: Feb 2015 • Databases: Medline, CENTRAL, Embase, trial registries • Study designs: RCTs • N included studies: N=0 RCTs	• Eligibility criteria: adults (aged 18 years and over) receiving palliative care suffering from nausea or vomiting, or both • Exclusion: nausea or vomiting thought to be secondary to pregnancy or surgery; studies of levomepromazine for the control of nausea or vomiting associated with chemotherapy were excluded unless all the participants (or a specified subgroup, analysed separately) were receiving palliative care	Levomepromazine	-	• Duplicate selection • No language restriction
Davis 2010	• Design: systematic review	• Eligibility criteria: adults with active cancer, treatment for nausea	Antiemetics	• See below for results of included studies	• Limited to English language

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Funding: not reported; CoI: not reported • Search date: 2008 • Databases: PubMed, OVID Medline, CENTRAL, ProQuest • Study designs: RCTs, prospective trials, cohort studies, case series, single-case reports • N included studies: N=14 RCTs	and vomiting clinically determined to be related to the cancer or as a complication from the cancer			• Unclear if review process was done by independent reviewers • Quality appraisal using Jadad scale • Relevant included studies: Bruera 2000, Corli 1995
Dietz 2013	• Design: systematic review • Funding: unclear; CoI: none • Search date: Apr 2012 • Databases: Medline, Embase, The Cochrane Library, PsychInfo, Ovid Nursing • Study designs: RCTs, prospective trials, cohort studies, case series, case	• Eligibility criteria: adults treated in the palliative care setting; pharmacological treatment of symptoms at the end of life with levomepromazine	Levomepromazine	-	• Limited to English language • Duplicate selection • Unclear if data extraction was done by independent reviewers

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	reports, systematic reviews • N included studies: N=0 RCTs				
Doppen 2022	• Design: systematic review • Funding: none; CoI: none • Search date: Sep 2021 • Databases: PubMed, Embase, The Cochrane Library, clinicaltrials.gov • Study designs: all • N included studies: N=20 RCTs	• Eligibility criteria: primary research in children and/or adults prescribed medicinal cannabis product (plant-derived or synthetically manufactured), in any formulation or dose, for symptoms due to a terminal disease • Exclusion: study population was not clearly specified as being “palliative”, “advanced”, “end-stage” or “incurable”; the medicinal cannabis was not prescribed	Medicinal cannabis	• See below for results of Brisbois 2011	• Study selection, data extraction and quality appraisal done by independent reviewers • Restricted to English language • Relevant included RCTs: Brisbois 2021
Douglas 2009	• Design: systematic review • Funding: unclear; CoI: unclear • Search date: May 2006 • Databases: Medline, Embase, Cinahl	• Eligibility criteria: patients dying with chronic kidney disease • Exclusion: articles which did not relate to the management of symptoms in adult renal populations and those which described	Symptom management	-	• Unclear if review process was done by independent researchers • Unclear language restriction

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Study designs: all • N included studies: N=0 RCTs	management of symptoms yet thought to be less relevant in the last days of life			
Economos 2020	• Design: systematic review • Funding: King's College London; CoI: none • Search date: Jan 2019 • Databases: Medline, • Scopus, Web of Science, Central and EMBASE, trial registers • Study designs: all • N included studies: N=3 RCTs	• Eligibility criteria: patients diagnosed with cancer, excluding cancer survivors, with one or more of the following symptoms: depression, anxiety, sleep disorders, nausea, anorexia, weight loss, breathlessness, pain, constipation, fatigue and drowsiness	Mirtazapine	-	• Unclear if study selection was done by independent researchers • Data extraction and quality appraisal done by independent researchers • Restricted to English and French literature • Relevant included RCTs: Cao 2018 (but published as an abstract)
Glare 2004	• Design: systematic review • Funding: Strategic Research Development grant from NHMRC; CoI: unclear • Search date: June 2003 • Databases: US Clinical Guidelines Repository,	• Eligibility criteria: patients with cancer in an advanced stage and with nausea • Exclusion: study objective was aimed at evaluating (a) antiemetics for the control of nausea and vomiting caused by emetogenic chemotherapy, or (b)	Antiemetics	• See below for results of included studies	• Unclear if study selection was done by independent researchers • Data extraction done by one researcher • Restricted to English literature • Quality appraisal with MERGE instrument • Relevant included studies: Bruera 2000

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Cochrane Library, Medline, Embase • Study designs: systematic reviews, RCT, phase I/II clinical trials, well-designed cohort/case-control studies and case series • N included studies: N=7 RCTs	agents for the treatment of bowel obstruction other than the standard antiemetics (such as surgery, tubes, or drugs intended to control secretions such as hyoscine or octreotide)			
Miller 2014	• Design: systematic review • Funding: unclear; CoI: none • Search date: Oct 2012 • Databases: Medline, Cinahl • Study designs: any experimental design • N included studies: N=6 RCTs	• Eligibility criteria: anorexia in adult palliative care for malignant or nonmalignant, life-limiting conditions	Corticosteroids	• See below for results of included studies	• Study selection and quality appraisal done by independent reviewers • Unclear if data extraction was done by independent researchers • Evidence grading with SIGN system • Restricted to English literature • Relevant included studies: Popiela 1989
Mucke 2018	• Design: systematic review + meta-analysis • Funding: Commonwealth	• Eligibility criteria: participants of any age, diagnosed with any advanced or end-stage medical disease (e.g.	Cannabinoids	• See below for results of Brisbois 2011	• Review process by independent reviewers • Language restriction unclear

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Department of Health, the NSW Government Centre for Medicinal Cannabis Research and Innovation, the Victorian Department of Health and Human Services and the Queensland Department of Health; NHMRC research fellowship #1041472; the Australian Government under the Substance Misuse Prevention and Service Improvements Grant Fund"; Col: none • Search date: Mar 2017 • Databases: CENTRAL, Medline, PsycINFO, PubMed, and Scopus	cancer, dementia, HIV/Acquired Immune Deficiency Syndrome (AIDS), heart disease, lung disease, and liver disease) • Exclusion: non-randomized studies, short abstracts, case reports, and studies without focus on palliative care aspects; studies on neuropathic pain in patients with HIV			• Complete GRADE process used • Relevant included RCTs: Brisbois 2021

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Study designs: RCTs • N included studies: N=9 RCTs				
Murray-Brown 2015	• Design: systematic review • Funding: unclear; CoI: none • Search date: Nov 2014 • Databases: Medline, CENTRAL, Embase, Cinahl, AMED, trial registries • Study designs: RCTs • N included studies: N=1 RCTs	• Eligibility criteria: adults receiving palliative care or suffering from an incurable progressive medical condition, and suffering from nausea or vomiting, or both • Exclusion: nausea or vomiting, or both, thought to be secondary to pregnancy or surgery	Haloperidol	-	• Duplicate selection • No language restriction • No relevant RCTs
Sande 2019	• Design: systematic review • Funding: none; CoI: none • Search date: Nov 2017 • Databases: Medline, Embase • Study designs: RCTs • N included studies: N=15 RCTs	• Eligibility criteria: patients with cancer; at least 18 years of age; on opioids (weak or strong opioid) as defined by WHO's Analgesic Ladder for cancer pain relief; nausea and/or vomiting assessed as a primary or secondary outcome • Exclusion: nausea and vomiting related to chemotherapy,	Management of opioid-induced nausea and vomiting	• See below for results of included studies	• Restricted to English literature • Unclear if study selection was done by independent reviewers • Data extraction and quality appraisal done by independent reviewers • GRADE process used • No relevant RCTs

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		radiotherapy, malignant bowel obstruction, or postoperative settings			
Solmi 2023	• Design: systematic review • Funding: none; CoI: extensive list in article • Search date: Feb 2022 • Databases: PubMed, PsychInfo, Embase, Cochrane Library • Study designs: meta-analyses • N included studies: N=0 RCTs	• Eligibility criteria: meta-analyses of observational studies (ie, case-control and cohort studies) and randomised controlled trials that reported on any outcome associated with cannabis and cannabinoids use in humans • Exclusion: systematic reviews without a meta-analysis, meta-analyses of risk factors for cannabinoids use, meta-analyses of cross-sectional studies only, pooled analyses of studies identified without a systematic search, and individual studies	Cannabis	-	• Duplicate study selection and data extraction • No language restriction • Quality appraisal using Amstar instrument • No relevant included studies
Storrar 2014	• Design: systematic review • Funding: Cochrane Collaboration; CoI: none	• Eligibility criteria: adults receiving palliative care or suffering from an incurable progressive medical condition, and	Droperidol	-	• Duplicate selection • No language restriction

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Search date: Nov 2013 • Databases: Medline, Embase, CENTRAL, AMED, Cinahl, trial registers • Study designs: RCTs • N included studies: N=0 RCTs	suffering from nausea or vomiting, or both • Exclusion: nausea or vomiting, or both, thought to be secondary to pregnancy or surgery; antiemetic(s) used for the prophylaxis of nausea or vomiting associated with chemotherapy			
Sutherland 2018	• Design: systematic review • Funding: Health Education Thames Valley; CoI: none • Search date: Sep 2017 • Databases: CENTRAL, Medline, Embase • Study designs: RCTs • N included studies: N=14 RCTs	• Eligibility criteria: patients with cancer (of any type or stage), who had nausea and vomiting treated with olanzapine, or where olanzapine was used to prevent nausea and vomiting • Exclusion: studies in which olanzapine was used for the treatment or prevention of nausea and vomiting in non-cancer patients	Olanzapine	• See below for results of Navari 2010	• Review process by independent reviewers • No language restriction • Relevant included studies: Navari 2010
Tramer 1999	• Design: systematic review • Funding: PROSPER research grant from the Swiss National Science	• Eligibility criteria: prophylactic efficacy of antiemetic interventions compared with placebo or no treatment in patients with acute,	Prophylactic antiemetics during patient-controlled analgesia therapy	-	• Unclear if study selection was done by independent reviewers • Data extraction and quality appraisal

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Foundation (Grant No 3233–051939.97); Col: unclear • Search date: Apr 1998 • Databases: Medline, Embase, Cochrane Library • Study designs: RCTs • N included studies: N=14 RCTs	postoperative pain treated with a PCA device containing an opioid • Exclusion: abstracts, letters, and review articles; interventions to treat established postoperative nausea and vomiting			done by independent reviewers • No language restriction • Quality appraisal using Jadad scale • No relevant included studies
Vayne-Bossert 2017	• Design: systematic review • Funding: Mater Research - The University of Queensland, School of Pharmacy and Menzies Health Institute Queensland, GriFith University, The Mater Palliative Care Research Fund and St Vincent's Hospital Brisbane, Australia; Col: none	• Eligibility criteria: participants with cancer suffering from nausea, vomiting or both not related to chemotherapy, radiotherapy, or surgery, aged 18 years and above	Corticosteroids	• See below for results of included studies	• Review process by independent reviewers • No language restriction • No relevant RCTs

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Search date: Aug 2016 • Databases: CENTRAL, Medline, Embase, Cinahl, EBSCO, Web of Science, LILACS, Conference Proceedings Citation Index, trial registries • Study designs: RCTs • N included studies: N=3 RCTs				

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Brisbois 2011	• Design: RCT • Funding: Canadian Institutes of Health Research (CIHR) (MOP 85060, MOP 86497) and the Alberta Cancer Board (ACB) (0051-71790124); Alberta Heritage	• Eligibility criteria: adult patients with advanced cancer (defined as locally recurrent, locally advanced, or metastatic) of any site except brain who had a score at least 2 (out of 16) on a scored Taste and Smell Survey;	Delta-9-Tetrahydrocannabinol (2.5 mg/day to a max of 20 mg/day) (N=24) vs. Placebo (N=22)	CRITICAL OUTCOMES • Nausea / vomiting: 11-point Edmonton Symptom Assessment System ○ "Nausea scores were unaffected by THC treatment (p=0.532)" • Quality of life: Functional Assessment of Anorexia/Cachexia	Level of evidence: high risk of bias • Randomisation by third party pharmacist according to a third-party computer-generated

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Foundation for Medical Research, Natural Sciences and Engineering Research Council of Canada, CIHR, and ACB; CoI: Solvay Pharma Inc. (Markham, ON, Canada) provided the drug, placebo, and third party monitor • Setting: 2 centres, Canada • Sample size: N=46 • Duration: 30-day follow-up; recruitment 2006-2008	decreased food intake for at least 2 weeks (reported by subject or physician) and a physician-assessed life expectancy of >2 months • Exclusion criteria: enteral or parenteral nutrition; allergies or sensitivity to THC and/or sesame seed oil; history of substance abuse (determined by review of patients' medical records, alcohol abuse was often also assessed by CAGE questionnaire) or psychotic episodes (e.g. diagnosis of schizophrenia or psychosis); mechanical obstruction of alimentary tract, mouth, or nose; radiation therapy to the head/neck; primary brain tumor; nausea score >5 on 11-point scale (0 = no nausea, 10 = worst possible nausea); medical		Therapy (FAACT) questionnaire, global score (SE), at 18 days ○ 98.5 (6.1) vs. 101.8 (6.1), p=0.704 • Patient satisfaction: not reported • Adverse events: ○ No differences were reported during the trial or within the 30-day follow-up period between THC and placebo groups for the number of adverse events or serious adverse events (p=0.622 and p=0.244, respectively) • Completion of chemotherapy: not reported • Overall survival: not reported • Progression-free survival: not reported	randomization scheme • Double-blinded, but unclear if assessors were blinded • 21/46 randomised patients included in analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		conditions affecting chemosensory function (i.e. infection of the mouth or nasal cavity, active sinusitis, hay fever), history of tachyarrhythmias, angina pectoris, or uncontrolled hypertension; liver impairment determined by Child-Pugh score >= 10; use of marijuana within 30 days before start of trial; treatments with the specific intention of increasing appetite or anabolism • *A priori* patient characteristics: ○ Mean age: 67.0 vs. 65.5y ○ M/F: 12/9 ○ Cancer type: lung N=10, genitourinary N=5, gastrointestinal N=4 ○ Nausea score at inclusion (11-point scale): 1.5 vs. 0.9			
Bruera 2000	• Design: cross-over RCT	• Eligibility criteria: adult patients over 18 years of	Controlled-release	CRITICAL OUTCOMES	Level of evidence: high risk of bias

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Funding: unclear; CoI: unclear • Setting: single cancer centre, US • Sample size: N=26 • Duration: 9 days	age with a history of more than 1 month of cancer-associated dyspepsia, characterized by nausea (minimum score of 2 in a 0–4 categorical scale) and at least a score of 1 on anorexia, early satiety, bloating, or vomiting/retching; presence of mental and physical competence to provide informed consent, ability to complete a daily patient diary, and absence of any other prokinetic, antinauseant, or antiemetic therapy before entrance to the study • Exclusion criteria: history of allergy or significant toxicity to metoclopramide or dimenhydrinate, mechanical bowel obstruction, ileostomy/colostomy, obvious thrush, severe	metoclopramide 40 mg every 12 hours for 4 days (N=26) vs. Matching placebo (N=26)	• Nausea / vomiting: VAS ○ Nausea intensity: 12 vs. 17, p=0.0426 ○ Vomiting intensity: 9 vs. 14 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: ○ The frequency and severity of elicited adverse events did not differ between treatments ○ Only 3 patients during the CRM phase and 5 patients during the placebo phase reported unelicited side effects ○ In no case was it necessary to discontinue CRM because of toxicity • Completion of chemotherapy: not reported • Overall survival: not reported • Progression-free survival: not reported	• Patients were randomized to each phase by a computer-generated code that was kept sealed in the pharmacy • Double-blinded, but unclear if assessors were blinded • Reduction of dose to 20 mg was possible • Rescue antinausea doses of dimenhydrinate 50 mg every 3–4 hours as needed • 6/26 patients excluded from analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		constipation, brain metastases, or patients scheduled to receive chemotherapy or radiation therapy to the abdomen or other areas likely to provoke gastrointestinal symptoms • *A priori* patient characteristics: ○ Mean age: 62y ○ M/F: 9/17 ○ Cancer type: breast N=8, gastrointestinal N=4, lung N=4, genitourinary N=4			
Corli 1995	• Design: cross-over RCT • Funding: not reported; CoI: not reported • Setting: palliative care unit, Italy • Sample size: N=30 • Duration: unclear	• Eligibility criteria: patients with advanced cancer who were no longer undergoing treatment with chemotherapy and were receiving only palliative care; at least 48h of continued and highly intense nausea or vomiting or both • Exclusion criteria: patients who were still receiving palliative	Levosulpiride 3x25 mg/day IM for 7 days (N=30) vs. Metoclopramide 3x10 mg/day IM for 7 days (N=30)	CRITICAL OUTCOMES • Nausea / vomiting: ○ Disappearance of nausea: 84.6% vs. 42.3%, p=0.0034 ○ Number of hours with nausea: 1.08 vs. 2.01 h/day, p=0.002 ○ Nausea intensity (Overall Nausea Index, mean per day): 0.757 vs. 1.418, p=0.0004 ○ Emesis control: 81.5% vs. 51.8%, p=0.041 ○ Average number of vomiting episodes per day: 0.385 vs. 0.698, p=0.002	Level of evidence: unclear risk of bias • Method of randomisation and allocation concealment not reported • Double-blinded, but unclear if assessors were blinded • 29/30 patients included in analysis, although the data suggest otherwise

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		radiotherapy; bowel obstruction • *A priori* patient characteristics: ○ Cancer type: lung N=4, gastrointestinal N=7, hepatobiliary N=6, genitourinary N=8, breast N=3		• Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported • Completion of chemotherapy: not reported • Overall survival: not reported • Progression-free survival: not reported	
Hardy 2018	• Design: RCT • Funding: Palliative Care Clinical Studies Collaborative and funded by the National Health and Medical Research Council of Australia; CoI: several interests reported in the article • Setting: 11 centres, Australia • Sample size: N=181 • Duration: outcomes measured at 72h; recruitment Oct 2010 – Apr 2014	• Eligibility criteria: participants > 18 years, had a diagnosis of cancer and nausea with an average score of ≥3 on an 11 point (0-10) NRS, not currently receiving antiemetics or had received inappropriate antiemetics • Exclusion criteria: had a short term iatrogenic or reversible cause of nausea for which there was high level evidence that a specific antiemetic or intervention was indicated (e.g., raised intracranial pressure or acute chemo-radiotherapy induced nausea), were likely to	Antiemetic therapy based on etiology-based clinical practice guidelines (N=95) vs. Haloperidol 1.0 mg/24h (to maximum 3.0 mg/24h) (N=86)	CRITICAL OUTCOMES • Nausea / vomiting: ○ Response at 72h: 49% vs. 53%, p=0.59 ○ Proportion of patients using rescue medication: ▪ At 24h: 33% vs. 42%, p=0.25 ▪ At 48h: 22% vs. 43%, p=0.003 ▪ At 72h: 27% vs. 35%, p=0.31 ○ Percentage of participants reporting ≥1 episode of vomiting/day at 72h: 17% vs. 17% • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: number of adverse events graded worse at 72 h than at baseline ○ Drowsiness: 11 vs. 14 ○ Fatigue: 12 vs. 8 ○ Anticholinergic effects: 8 vs. 12 ○ Gastrointestinal upset: 10 vs. 10	Level of evidence: high risk of bias • Randomization schedules were computer-generated for each site at an independent central registry; schedules for each site were allocated in a 1:1 ratio in randomly allocated blocks of two or four; schedules held by the central registry were sent to each site in opaque sealed envelopes numbered in sequence; on notification of an eligible patient, the research coordinator at each site opened

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		undergo any procedure with the potential to affect nausea in the two days prior, or during the study period, had a definite contraindication to any of the study medications, a change in glucocorticoid dose within 48 h, or poor performance status (that would have rendered the participant unable to complete study requirements) • *A priori* patient characteristics: ○ Mean age: 68.1 vs. 69.3 ○ M/F: 34/61 vs. 23/63 ○ Cancer type: breat N=23, lung N=21, colorectal N=21, gynaecologic N=26		• Completion of chemotherapy: not reported • Overall survival: not reported • Progression-free survival: not reported	the next numbered envelope, allocated the patient to the guideline treatment or single therapy arm, and notified research staff and treating clinicians of the treatment group allocation • No blinding • Rescue medication: metoclopramide 10 mg • Response was defined as at least a 2-point reduction in average nausea score and a score < 3 for average nausea over the preceding 24 h, measured at 72 h on an 11-point numerical rating scale (NRS)
Hardy 2019	• Design: RCT • Funding: grant from the Australian Government's National Health and Medical Research Council	• Eligibility criteria: known to a palliative care team, were >18 years, had a diagnosis of cancer and nausea with an average score over the past 24 hours of ≥3	Haloperidol 1.5-3 mg/day (N=59) vs. Methotrimeprazine 6.25-12.5 mg/day (N=57)	CRITICAL OUTCOMES • Nausea / vomiting: NRS ○ Response to treatment at 72h: 44/59 (75%) vs. 36/57 (63%), p=0.18 ○ Complete response: 33/59 (56%) vs. 29/57 (51%), p=0.59	Level of evidence: unclear risk of bias • Randomisation schedules were computer generated for each site at an

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	(NHMRC)-614247; CoI: none • Setting: 11 centres, Australia • Sample size: N=121 • Duration: recruitment Mar 2015 – Feb 2017	on an 11 point (0–10) numerical rating scale • Exclusion criteria: nausea related to the treatment of cancer (ie, surgery, chemotherapy) within 5 days of anticancer therapy, had nausea for which a specific antiemetic was indicated and randomisation to study medications alone would not be appropriate (such as dexamethasone for acutely raised intra-cranial pressure and 5HT3 antagonists for chemotherapy-induced or radiotherapy-induced N/V), were to undergo a procedure or intervention with the potential to affect nausea during the 3-day study period (such as radiotherapy to a site likely to cause nausea), had received methotrimeprazine or haloperidol at study		○ After treatment completion (72 hours), patients in both arms were significantly less distressed by nausea, compared with baseline, with estimated mean scores of 2.0 (95%CI 1.2-2.8) and 2.2 (95%CI 1.4-3.0) ○ Episodes of vomiting in past 24h: ▪ At 24h: 11/56 vs. 7/57, p=0.28 ▪ At 48h: 8/53 vs. 4/51, p=0.24 ▪ At 72h: 7/52 vs. 7/49, p=0.91 ○ Rescue doses: ▪ At 24h: 26/57 vs. 28/57 ▪ At 48h: 18/55 vs. 22/53 ▪ At 72h: 16/52 vs. 20/49 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: ○ Proportion of patients with at least 1 event (any grade): 29/52 vs. 31/49 ○ More participants in the methotrimeprazine arm reported drowsiness worse at 72 hours than at baseline (20% vs 12%), but this difference was not significant • Completion of chemotherapy: not reported • Overall survival: not reported • Progression-free survival: not reported	independent central registry • There was no stratification • Schedules for each site were allocated in a 1:1 ratio in randomly allocated blocks of 2 and 4 and sent to each site pharmacy • All capsules were opaque and looked identical to preserve the blinding irrespective of the contents • Treatment allocation was not disclosed to study staff, treating clinicians or investigators until data cleaning was complete • 5/121 patients excluded from analysis • Response was defined as at least a two-point reduction in average nausea score from baseline over the preceding 24

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		doses within the previous 48 hours, a change in glucocorticoid dose within 48 hours, or poor performance status • *A priori* patient characteristics: ○ Mean age: 66.2 vs. 67.9y ○ M/F: 25/34 vs. 17/40 ○ Cancer type: lung N=19, breast N=18, gynaecologic N=18, prostate N=10			hours, measured at 72 hours on an 11-point NRS; complete response was defined as at least a two-point reduction in average nausea score from baseline over the preceding 24 hours with a final score <3/10
Navari 2010	• Design: RCT • Funding: Walther Cancer Foundation and the Reich Family Endowment for the care of the whole patient; CoI: not reported • Setting: single cancer centre, US • Sample size: N=80 • Duration: recruitment Mar 2005 – Dec 2007	• Eligibility criteria: patients at least 18 years of age with histologically or cytologically confirmed advanced gastrointestinal or lung cancer, stages III–IV, with anorexia, cancer-related loss of appetite, and cancer-related loss of preillness stable weight (greater than or equal to 5%); no major surgery, chemotherapy, or radiotherapy in the previous 4 weeks; no active dysphagia or	Oral megestrol acetate 800 mg/day (N=40) vs. Oral megestrol acetate 800 mg/day plus oral olanzapine 5 mg/day (N=40)	CRITICAL OUTCOMES • Nausea / vomiting: ○ N patients with nausea improvement (MDASI): ▪ At 4w: 5 vs. 21 ▪ At 8w: 3 vs. 23 ○ Nausea NDASI score: ▪ At 4w: 5.7 vs. 2.1, p<0.01 ▪ At 8w: 6.3 vs. 1.8, p<0.01 • Quality of life: ○ N patients with quality of life improvement (MDASI): ▪ At 4w: 7 vs. 29 ▪ At 8w: 5 vs. 23 • Patient satisfaction: not reported • Adverse events:	Level of evidence: high risk of bias • Method of randomization and allocation concealment unclear • No blinding • Patients were removed from the study if they did not take the study medication for a 48-h period or developed an adverse toxicity attributed to the study agents

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		gastrointestinal tract obstruction; no history of thrombophlebitis and no systemic corticosteroids in the previous 4 weeks; serum creatinine less than or equal to 2.0 mg/dl; serum bilirubin less than or equal to 2.0 mg/dl; serum glutamic oxaloacetic transaminase or serum glutamic pyruvic transaminase less than or equal to three times upper limits of normal; absolute neutrophil count greater than or equal to 1,500 mm3; patients of childbearing potential (male and female) must consent to use adequate contraception throughout protocol therapy; females of childbearing potential must have a negative urine pregnancy test; no severe cognitive compromise; no known		○ There were no grade III or IV toxicities attributable to the study drugs in any of the patients receiving MA or MA plus OLN ○ There were no episodes of deep vein thromboses ○ Only two patients had evidence of mild sedation, possibly related to the OLN • Completion of chemotherapy: not reported • Overall survival: not reported • Progression-free survival: not reported	• 4/80 patients not included in analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		history of central nervous system disease (e.g., brain metastases, seizure disorder); no treatment with another antipsychotic agent such as risperidone, quetiapine, clozapine, phenothiazine, or butyrophenone for 30 days prior to or during protocol therapy; chronic phenothiazine administration as an antipsychotic agent was not allowed, but patients may receive prochloperazine and other phenothiazines as antiemetic therapy; no concurrent use of ethyol; no concurrent abdominal radiotherapy; no concurrent use of quinolone antibiotic therapy; no chronic alcoholism (as determined by the investigator); no known hypersensitivity to OLN; no known cardiac			

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		arrhythmia, uncontrolled congestive heart failure or acute myocardial infarction within the previous 6 months; and no history of uncontrolled diabetes mellitus • *A priori* patient characteristics: ○ Median age: 63y ○ M/F: 43/37 ○ Cancer type: colon stage III N=20, colon stage IV N=15, lung stage III N=21, lung stage IV N=24			
Popiela 1989	• Design: RCT • Funding: not reported; CoI: not reported • Setting: international multicentre study (N=13) • Sample size: N=173 • Duration: 8 weeks follow-up	• Eligibility criteria: female patients with advanced, terminal cancer, and with pain, debility, nausea, cachexia, etc.; no further anticancer therapy anticipated; minimum expected survival time of at least 2 months from study enrollment; willing to consent to participate according to local custom	Methylprednisolone sodium succinate 125 mg/day IV for 56 days (N=85) vs. Matching placebo (N=88)	CRITICAL OUTCOMES • Nausea / vomiting: LASA scores, only presented in graphs ○ Vomiting and nausea showed consistent, often statistically significant, improvement across time in the MPSS-treated patients when compared with the placebo group ○ The frequency of antinauseant administration did not differ within the two treatment groups at any point during the study	Level of evidence: unclear risk of bias • Computer-generated randomization scheme • Double-blinded: blinded packages with vials of study medication; unclear if assessors were blinded • Many outcomes only presented in graphs

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		• Exclusion criteria: concurrent corticosteroid therapy or corticosteroid therapy of greater than 2 weeks duration within 1 month of study enrollment; anticancer therapy within 2 weeks of study enrollment; pregnancy; active peptic ulcer or evidence of gastrointestinal bleeding; systemic fungal infection; active TB; uncontrolled diabetes mellitus; acute febrile illness; psychosis; abnormal mental status which could interfere with completion of subjective evaluations; neoplastic disease other than solid tumors • A priori patient characteristics: ○ Mean age: 64.9 vs. 65.8y		• Quality of life: only presented in graph ○ Combined LASA scores for the steroid patients were significantly better than those of the placebo patients at all follow-up weeks except weeks 1 and 6 • Patient satisfaction: not reported • Adverse events: ○ Reported infectious complications were comparable between treatment groups (11.8% MPSS; 14.8% placebo) ○ A combined total of 145 medical events were reported by 54 (63.5%) MPSS patients and 47 (53.4%) placebo patients; these events were classified as cardiovascular, gastrointestinal, shock/respiratory failure, infection/inflammation, metabolic, unrelated to investigational therapy, or other ○ There were significantly more gastrointestinal (9/85, 10.6% MPSS; 2/88, 2.2% placebo, $p<0.05$) and cardiovascular (7/85,8.2% MPSS; 1/88, 1.1% placebo, $p<0.05$) side-effects reported in the steroid group ○ Although significantly more of the adverse events were felt to be	

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				either related or probably related to investigational therapy (21% MPSS; 1% placebo, p<0.05), there were no differences between treatments with regard to the severity of the event, as assessed by the investigator, or its ultimate outcome • Completion of chemotherapy: not reported • Overall survival: only presented in graph ○ No significant differences between treatment groups with regard to overall mortality during the 8-week study follow-up period ○ No significant differences between treatments with regard to time to death • Progression-free survival: not reported	

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; CRM: controlled-release metoclopramide; FAACT: Functional Assessment of Anorexia/Cachexia Therapy; IM: intramuscular; LASA: Linear Analogue Scale Assessment; MA: megestrol acetate; MDASI: M.D. Anderson Symptom Inventory; MPSS: methylprednisolone sodium succinate; NRS: numeric rating scale; OLN: olanzapine; PCA: patient-controlled analgesia; RCT: randomised controlled trial; SE: standard error; THC: tetrahydrocannabinol.

References

Brisbois, T.D., et al., Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Annals of Oncology, 2011. 22(9): p. 2086-2093.

Bruera E, Belzile M, Neumann C, et al. A double-blind, crossover study of controlled-release metoclopramide and placebo for the chronic nausea and dyspepsia of advanced cancer. J Pain Symptom Manage 2000;19(6):427-435.

Cao J, Wang B, Wang Z et al (2018) Efficacy of mirtazapine in preventing delayed nausea and vomiting induced by highly emetogenic chemotherapy: an open-label, randomized, multicenter phase III trial. J Clin Oncol 36:1078–1078.

Corli, O., A. Cozzolino, and L. Battaiotto, Effectiveness of levosulpiride versus metoclopramide for nausea and vomiting in advanced cancer patients: A double-blind, randomized, crossover study. Journal of Pain and Symptom Management, 1995. 10(7): p. 521-526.

Cox, L., E. Darvill, and S. Dorman, Levomepromazine for nausea and vomiting in palliative care. Cochrane Database of Systematic Reviews, 2015(11): p. CD009420.

Davis M, Hallerberg G. A systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy of radiation. Journal of Pain and Symptom Management 2010;39(4):756-67.

Dietz, I., et al., Evidence for the use of Levomepromazine for symptom control in the palliative care setting: A systematic review. BMC Palliative Care, 2013. 12(1).

Doppen, M., et al., Cannabis in Palliative Care: A Systematic Review of Current Evidence. Journal of Pain & Symptom Management, 2022. 64(5): p. e260-e284.

Douglas, C., et al., Symptom management for the adult patient dying with advanced chronic kidney disease: a review of the literature and development of evidence-based guidelines by a United Kingdom Expert Consensus Group. Palliative Medicine, 2009. 23(2): p. 103-10.

Economos, G., et al., What is the evidence for mirtazapine in treating cancer-related symptomatology? A systematic review. Supportive Care in Cancer, 2020. 28(4): p. 1597-1606.

Glare, P., et al., Systematic review of the efficacy of antiemetics in the treatment of nausea in patients with far-advanced cancer. Supportive Care in Cancer, 2004. 12(6): p. 432-40.

Hardy, J., et al., A randomized open-label study of guideline-driven antiemetic therapy versus single agent antiemetic therapy in patients with advanced cancer and nausea not related to anticancer treatment. BMC Cancer, 2018. 18(1): p. 510.

Hardy, J.R., et al., Methotrimeprazine versus haloperidol in palliative care patients with cancer-related nausea: a randomised, double-blind controlled trial. BMJ Open, 2019. 9(9): p. e029942.

Miller, S., et al., Use of corticosteroids for anorexia in palliative medicine: A systematic review. Journal of Palliative Medicine, 2014. 17(4): p. 482-485.

Mucke, M., et al., Systematic review and meta-analysis of cannabinoids in palliative medicine. Journal of Cachexia, Sarcopenia and Muscle, 2018. 9(2): p. 220-234.

Murray-Brown, F. and S. Dorman, Haloperidol for the treatment of nausea and vomiting in palliative care patients. Cochrane Database of Systematic Reviews, 2015(11): p. CD006271.

Navari, R.M. and M.C. Brenner, Treatment of cancer-related anorexia with olanzapine and megestrol acetate: a randomized trial. Supportive Care in Cancer, 2010. 18(8): p. 951-6.

Popiela T, Lucchi R, Giongo F: Methylprednisolone as palliative therapy for female terminal cancer patients. Eur J Cancer Clin Oncol 1989;25:1823–1829.

Sande, T.A., B.J.A. Laird, and M.T. Fallon, The Management of Opioid-Induced Nausea and Vomiting in Patients with Cancer: A Systematic Review. Journal of Palliative Medicine, 2019. 22(1): p. 90-97.

Solmi, M., et al., Balancing risks and benefits of cannabis use: umbrella review of meta-analyses of randomised controlled trials and observational studies. BMJ, 2023. 382: p. e072348.

Storrar, J., et al., Droperidol for treatment of nausea and vomiting in palliative care patients. Cochrane Database of Systematic Reviews, 2014(11): p. CD006938.

Sutherland, A., et al., Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults. Cochrane Database of Systematic Reviews, 2018. 9: p. CD012555.

Tramer MR, Walder B. Efficacy and adverse effects of prophylactic antiemetics during patient-controlled analgesia therapy: a quantitative systematic review. Anesthesia and Analgesia 1999;88:1354-61.

Vayne-Bossert, P., et al., Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery). Cochrane Database of Systematic Reviews, 2017. 7: p. CD01200

GRADE-profielen

Auteur(s): Bruera E, Belzile M, Neumann C, et al. A double-blind, crossover study of controlled-release metoclopramide and placebo for the chronic nausea and dyspepsia of advanced cancer. J Pain Symptom Manage 2000;19(6):427-435.

Vraagstelling: CR metoclopramide versus placebo for adult patients with cancer-associated dyspepsia

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	CR metoclopramide	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Nausea VAS score												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[b]	niet gevonden	20	20	-	SMD **0.44 lager** (1.07 lager tot 0.18 hoger)	⨁⨁◯◯ Laag[a,b]	CRUCIAAL
Vomiting VAS score												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	CR metoclopramide	placebo	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[b]	niet gevonden	20	20	-	SMD **0.44 lager** (1.07 lager tot 0.19 hoger)	⨁⨁◯◯ Laag[a,b]	CRUCIAAL

Frequency of administration (doses/day) of rescue medication

1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[c]	niet gevonden	20	20	-	SMD **0** (0.62 lager tot 0.62 hoger)	⨁◯◯◯ Zeer laag[a,c]	BELANGRIJK

Quality of life - niet gerapporteerd

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	CR metoclopramide	placebo	Relatief (95% CI)	Absoluut (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

Patient satisfaction - niet gerapporteerd

-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

Proportion of patients with unelicited side effects

1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	3/20 (15.0%)	5/20 (25.0%)	**RR 0.60** (0.17 tot 2.18)	**100 minder per 1.000** (from 208 minder tot 295 meer)	⨁◯◯◯ Zeer laag[a,d]	BELANGRIJK

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	CR metoclopramide	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Completion of chemotherapy - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK
Overall survival - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK
Progression-free survival - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1.1.1.5 Explanations

a. Bruera 2000: unclear blinding of assessors, no ITT analysis

b. CI around SMD includes -0.5

c. CI around SMD includes -0.5 and 0.5

d. CI around RR includes 0.75 and 1.25

Auteur(s): Hardy, J., et al., A randomized open-label study of guideline-driven antiemetic therapy versus single agent antiemetic therapy in patients with advanced cancer and nausea not related to anticancer treatment. BMC Cancer, 2018. 18(1): p. 510.

Vraagstelling: Guideline-driven antiemetic therapy versus haloperidol voor adult patients with cancer and nausea

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	guideline-driven antiemetic therapy	haloperidol	Relatief (95% CI)	Absoluut (95% CI)		
Proportion of patients with nausea response at 72h												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	guideline-driven antiemetic therapy	haloperidol	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[b]	niet gevonden	47/95 (49.5%)	46/86 (53.5%)	**RR 0.92** (0.70 tot 1.23)	**43 minder per 1.000** (from 160 minder tot 123 meer)	⨁⨁◯◯ Laag[a,b]	CRUCIAAL

Proportion of patients using rescue medication at 24h

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	guideline-driven antiemetic therapy	haloperidol	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[c]	niet ernstig	niet ernstig	ernstig[b]	niet gevonden	30/92 (32.6%)	34/82 (41.5%)	**RR 0.79** (0.53 tot 1.16)	**87 minder per 1.000** (from 195 minder tot 66 meer)	⨁⨁◯◯ Laag[b,c]	CRUCIAAL

Proportion of patients using rescue medication at 48h

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	guideline-driven antiemetic therapy	haloperidol	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[c]	niet ernstig	niet ernstig	ernstig[b]	niet gevonden	18/83 (21.7%)	32/75 (42.7%)	**RR 0.51** (0.31 tot 0.83)	**209 minder per 1.000** (from 294 minder tot 73 minder)	⨁⨁◯◯ Laag[b,c]	CRUCIAAL

Proportion of patients using rescue medication at 72h

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	guideline-driven antiemetic therapy	haloperidol	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[c]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	20/74 (27.0%)	26/75 (34.7%)	**RR 0.78** (0.48 tot 1.27)	**76 minder per 1.000** (from 180 minder tot 94 meer)	⨁◯◯◯ Zeer laag[c,d]	CRUCIAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	guideline-driven antiemetic therapy	haloperidol	Relatief (95% CI)	Absoluut (95% CI)		
Percentage of participants reporting ≥1 episode of vomiting/ day at 72h												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	guideline-driven antiemetic therapy	haloperidol	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[c]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	13/74 (17.6%)	13/75 (17.3%)	**RR 1.01** (0.50 tot 2.04)	**2 meer per 1.000** (from 87 minder tot 180 meer)	⨁◯◯◯ Zeer laag[c,d]	CRUCIAL

Quality of life - niet gerapporteerd

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	guideline-driven antiemetic therapy	haloperidol	Relatief (95% CI)	Absoluut (95% CI)		
–	–	–	–	–	–	–	–	–	–	–	–	CRUCIAL

Patient satisfaction - niet gerapporteerd												
–	–	–	–	–	–	–	–	–	–	–	–	CRUCIAAL
Adverse events												

1	gerandomiseerde trials	ernstig[c]	niet ernstig	niet ernstig	zeer ernstig[e]	niet gevonden	Number of adverse events graded worse at 72 h than at baseline: - Drowsiness: 11 vs. 14 - Fatigue: 12 vs. 8 - Anticholinergic effects: 8 vs. 12 - Gastrointestinal upset: 10 vs. 10				⊕◯◯◯ Zeer laag[c,e]	BELANGRIJK
Completion of												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	guideline-driven antiemetic therapy	haloperidol	Relatief (95% CI)	Absoluut (95% CI)		
chemotherapy - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK
Overall survival - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	guideline-driven antiemetic therapy	haloperidol	Relatief (95% CI)	Absoluut (95% CI)		
Progression-free survival - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

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

1.1.1.6 Explanations

a. Hardy 2018: no blinding

b. CI around RR includes 0.75

c. Hardy 2018: no blinding, no ITT analysis

d. CI around RR includes 0.75 and 1.25

e. No denominators reported

Auteur(s): Hardy, J.R., et al., Methotrimeprazine versus haloperidol in palliative care patients with cancer-related nausea: a randomised, double-blind controlled trial. BMJ Open, 2019. 9(9): p. e029942.

Vraagstelling: Haloperidol versus methotrimeprazine voor palliative cancer patients with nausea

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	haloperidol	methotrimeprazine	Relatief (95% CI)	Absoluut (95% CI)		
Nausea (NRS): response to treatment at 72h												
1	gerandomiseerde trials	niet ernstig	niet ernstig	niet ernstig	ernstig[a]	niet gevonden	44/59 (74.6%)	36/57 (63.2%)	**RR 1.18** (0.92 tot 1.51)	**114 meer per 1.000** (from 51 minder tot 322 meer)	⨁⨁⨁◯ Redelijk[a]	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	haloperidol	methotrimeprazine	Relatief (95% CI)	Absoluut (95% CI)		
Nausea (NRS): complete response												
1	gerandomiseerde trials	niet ernstig	niet ernstig	niet ernstig	ernstig[a]	niet gevonden	33/59 (55.9%)	29/57 (50.9%)	**RR 1.10** (0.78 tot 1.55)	**51 meer per 1.000** (from 112 minder tot 280 meer)	⨁⨁⨁◯ Redelijk[a]	CRUCIAAL
Distress caused by nausea at 24h												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	haloperidol	methotrimeprazine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[b]	niet ernstig	niet ernstig	ernstig[c]	niet gevonden	55	54	-	SMD **0.14 lager** (0.52 lager tot 0.24 hoger)	⨁⨁◯◯ Laag[b,c]	CRUCIAAL

Distress caused by nausea at 48h

1	gerandomiseerde trials	ernstig[b]	niet ernstig	niet ernstig	niet ernstig	niet gevonden	53	51	-	SMD **0** (0.38 lager tot 0.38 hoger)	⨁⨁⨁◯ Redelijk[b]	CRUCIAAL

Distress caused by nausea at 72h

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	haloperidol	methotrimeprazine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[b]	niet ernstig	niet ernstig	niet ernstig	niet gevonden	50	47	-	SMD **0.07 lager** (0.47 lager tot 0.33 hoger)	⨁⨁⨁◯ Redelijk[b]	CRUCIAAL

Episodes of vomiting in past 24h: at 24h

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	haloperidol	methotrimeprazine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	niet ernstig	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	11/56 (19.6%)	7/57 (12.3%)	**RR 1.60** (0.67 tot 3.83)	**74 meer per 1.000** (from 41 minder tot 348 meer)	⨁⨁◯◯ Laag[d]	CRUCIAAL

Episodes of vomiting in past 24h: at 48h

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	haloperidol	methotrimeprazine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[b]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	8/53 (15.1%)	4/51 (7.8%)	**RR 1.92** (0.62 tot 6.00)	**72 meer per 1.000** (from 30 minder tot 392 meer)	⨁◯◯◯ Zeer laag[b,d]	CRUCIAAL

Episodes of vomiting in past 24h: at 72h

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	haloperidol	methotrimeprazine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[b]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	7/52 (13.5%)	7/49 (14.3%)	**RR 0.94** (0.36 tot 2.49)	**9 minder per 1.000** (from 91 minder tot 213 meer)	⨁◯◯◯ Zeer laag[b,d]	CRUCIAAL

Proportion of patients using rescue antiemetics at 24h

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	haloperidol	methotrimeprazine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	niet ernstig	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	26/57 (45.6%)	28/57 (49.1%)	**RR 0.93** (0.63 tot 1.37)	**34 minder per 1.000** (from 182 minder tot 182 meer)	⨁⨁◯◯ Laag[d]	CRUCIAAL

Proportion of patients using rescue antiemetics at 48h

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	haloperidol	methotrimeprazine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[b]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	18/55 (32.7%)	22/53 (41.5%)	**RR 0.79** (0.48 tot 1.29)	**87 minder per 1.000** (from 216 minder tot 120 meer)	⨁◯◯◯ Zeer laag[b,d]	CRUCIAAL

Proportion of patients using rescue antiemetics at 72h

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	haloperidol	methotrimeprazine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[b]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	16/52 (30.8%)	20/49 (40.8%)	**RR 0.75** (0.44 tot 1.28)	**102 minder per 1.000** (from 229 minder tot 114 meer)	⨁◯◯◯ Zeer laag[b,d]	CRUCIAAL
Quality of life - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL
Patient satisfaction - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	haloperidol	methotrimeprazine	Relatief (95% CI)	Absoluut (95% CI)		
Proportion of patients with at least 1 event (any grade)												
1	gerandomiseerde trials	ernstig[b]	niet ernstig	niet ernstig	ernstig[e]	niet gevonden	29/52 (55.8%)	31/49 (63.3%)	**RR 0.88** (0.64 tot 1.22)	**76 minder per 1.000** (from 228 minder tot 139 meer)	⨁⨁◯◯ Laag[b,e]	BELANGRIJK
Completion of chemotherapy - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK
Overall survival - niet gerapporteerd												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	haloperidol	methotrimeprazine	Relatief (95% CI)	Absoluut (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

Progression-free survival - niet gerapporteerd

-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1.1.1.7 Explanations

a. CI around RR includes 1.25

b. Hardy 2019: no ITT analysis

c. CI around SMD includes -0.5

d. CI around RR includes 0.75 and 1.25

e. CI around RR includes 0.75

Auteur(s): Corli, O., A. Cozzolino, and L. Battaiotto, Effectiveness of levosulpiride versus metoclopramide for nausea and vomiting in advanced cancer patients: A double-blind, randomized, crossover study. Journal of Pain and Symptom Management, 1995. 10(7): p. 521-526.

Vraagstelling: Levosulpiride versus metoclopramide IM voor patients with advanced cancer and highly intense nausea and/or vomiting

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	**Studieopzet**	**Risk of bias**	**Inconsistentie**	**Indirect bewijs**	**Onnauwkeurigheid**	**Andere factoren**	**Levosulpiride**	**metoclopramide IM**	**Relatief (95% CI)**	**Absoluut (95% CI)**		
Disappearance of nausea												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[b]	niet gevonden	22/26 (84.6%)	11/26 (42.3%)	**RR 2.00** (1.24 tot 3.23)	**423 meer per 1.000** (from 102 meer tot 943 meer)	⨁⨁◯◯ Laag[a,b]	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Levosulpiride	metoclopramide IM	Relatief (95% CI)	Absoluut (95% CI)		
Number of hours with nausea (mean/day)												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[c]	niet gevonden	1.08 vs. 2.01 h/day, p=0.002				⨁◯◯◯ Zeer laag[a,c]	CRUCIAAL
Nausea intensity (mean per day)												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[c]	niet gevonden	0.757 vs. 1.418, p=0.0004				⨁◯◯◯ Zeer laag[a,c]	CRUCIAAL
Emesis control												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Levosulpiride	metoclopramide IM	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[b]	niet gevonden	22/27 (81.5%)	14/27 (51.9%)	**RR 1.57** (1.05 tot 2.36)	**296 meer per 1.000** (from 26 meer tot 705 meer)	⨁⨁◯◯ Laag[a,b]	CRUCIAAL

Average number of vomiting episodes per day

1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[c]	niet gevonden	0.385 vs. 0.698, p=0.002				⨁◯◯◯ Zeer laag[a,c]	CRUCIAAL

Quality of life - niet gerapporteerd

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Levosulpiride	metoclopramide IM	Relatief (95% CI)	Absoluut (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

Patient satisfaction - niet gerapporteerd

-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

Adverse events - niet gerapporteerd

-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

Completion of chemotherapy - niet gerapporteerd

-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

Overall survival - niet gerapporteerd

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Levosulpiride	metoclopramide IM	Relatief (95% CI)	Absoluut (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

Progression-free survival - niet gerapporteerd

-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

1.1.1.8 Explanations

a. Corli 1995: unclear method of randomisation and allocation concealment, unclear blinding of assessors, unclear ITT analysis (probably not)

b. CI around RR includes 1.25

c. Insufficient information to calculate precision, small sample size

Auteur(s): Popiela T, Lucchi R, Giongo F: Methylprednisolone as palliative therapy for female terminal cancer patients. Eur J Cancer Clin Oncol 1989;25:1823–1829.

Vraagstelling: Methylprednisolone versus placebo voor women with advanced terminal cancer

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	methylprednisolone	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Nausea / vomiting: LASA scores												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[b]	niet gevonden	Vomiting and nausea showed consistent, often statistically significant, improvement across time in the MPSS-treated patients when compared with the placebo group				⨁◯◯◯ Zeer laag[a,b]	CRUCIAAL
Antinauseant drugs												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[b]	niet gevonden	The frequency of antinauseant administration did not differ within the two treatment groups at any point during the study				⨁◯◯◯ Zeer laag[a,b]	CRUCIAAL
Quality of life: LASA score												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	methylprednisolone	placebo	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[b]	niet gevonden	Combined LASA scores for the steroid patients were significantly better than those of the placebo patients at all follow-up weeks except weeks 1 and 6				⨁◯◯◯ Zeer laag[a,b]	CRUCIAAL
Patient satisfaction - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL
Proportion of patients with at least one adverse event												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	methylprednisolone	placebo	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[c]	niet gevonden	54/85 (63.5%)	47/88 (53.4%)	**RR 1.19** (0.92 tot 1.53)	**101 meer per 1.000** (from 43 minder tot 283 meer)	⨁⨁◯◯ Laag[a,c]	BELANGRIJK

Infectious complications

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	methylprednisolone	placebo	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	10/85 (11.8%)	13/88 (14.8%)	**RR 0.80** (0.37 tot 1.72)	**30 minder per 1.000** (from 93 minder tot 106 meer)	⨁◯◯◯ Zeer laag[a,d]	BELANGRIJK

Gastrointestinal complications

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	methylprednisolone	placebo	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[c]	niet gevonden	9/85 (10.6%)	2/88 (2.3%)	**RR 4.66** (1.04 tot 20.94)	**83 meer per 1.000** (from 1 meer tot 453 meer)	⨁⨁◯◯ Laag[a,c]	BELANGRIJK
Cardiovascular complications												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[c]	niet gevonden	7/85 (8.2%)	1/88 (1.1%)	**RR 7.25** (0.91 tot 57.66)	**71 meer per 1.000** (from 1 minder tot 644 meer)	⨁⨁◯◯ Laag[a,c]	BELANGRIJK

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	methylprednisolone	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Completion of chemotherapy - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK
Overall survival												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[b]	niet gevonden	No significant differences between treatment groups with regard to overall mortality or time to death during the 8-week study follow-up period				⨁◯◯◯ Zeer laag[a,b]	BELANGRIJK
Progression-free survival - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

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

1.1.1.9 Explanations

a. Popiela 1989: unclear if outcome assessors were blinded, selective outcome reporting

b. No quantitative data reported, impossible to calculate precision

c. CI around RR includes 1.25

d. CI around RR includes 0.75 and 1.25

Auteur(s): Navari, R.M. and M.C. Brenner, Treatment of cancer-related anorexia with olanzapine and megestrol acetate: a randomized trial. Supportive Care in Cancer, 2010. 18(8): p. 951-6.

Vraagstelling: Oral megestrol acetate versus oral megestrol acetate plus olanzapine voor cancer-related anorexia

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	oral megestrol acetate	oral megestrol acetate plus olanzapine	Relatief (95% CI)	Absoluut (95% CI)		
Proportion of patients with nausea improvement (MDASI) at 4w												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	oral megestrol acetate	oral megestrol acetate plus olanzapine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	niet ernstig	niet gevonden	5/37 (13.5%)	21/39 (53.8%)	**RR 0.25** (0.11 tot 0.60)	**404 minder per 1.000** (from 479 minder tot 215 minder)	⨁⨁⨁◯ Redelijk[a]	CRUCIAAL

Proportion of patients with nausea improvement (MDASI) at 8w

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	oral megestrol acetate	oral megestrol acetate plus olanzapine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	niet ernstig	niet gevonden	3/37 (8.1%)	23/39 (59.0%)	**RR 0.14** (0.05 tot 0.42)	**507 minder per 1.000** (from 560 minder tot 342 minder)	⨁⨁⨁◯ Redelijk[a]	CRUCIAAL

Nausea MDASI score at 4w

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	oral megestrol acetate	oral megestrol acetate plus olanzapine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	niet ernstig	niet gevonden	37	39	-	SMD **2.35 hoger** (1.76 hoger tot 2.94 hoger)	⨁⨁⨁◯ Redelijk[a]	CRUCIAAL

Nausea MDASI score at 8w

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	oral megestrol acetate	oral megestrol acetate plus olanzapine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	niet ernstig	niet gevonden	37	39	-	SMD **1.83 hoger** (1.29 hoger tot 2.37 hoger)	⨁⨁⨁◯ Redelijk[a]	CRUCIAAL

Proportion of patients with quality of life improvement (MDASI) at 4w

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	oral megestrol acetate	oral megestrol acetate plus olanzapine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	niet ernstig	niet gevonden	7/37 (18.9%)	29/39 (74.4%)	**RR 0.25** (0.13 tot 0.51)	**558 minder per 1.000** (from 647 minder tot 364 minder)	⨁⨁⨁◯ Redelijk[a]	CRUCIAAL

Proportion of patients with quality of life improvement (MDASI) at 8w

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	oral megestrol acetate	oral megestrol acetate plus olanzapine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	niet ernstig	niet gevonden	5/37 (13.5%)	23/39 (59.0%)	**RR 0.23** (0.10 tot 0.54)	**454 minder per 1.000** (from 531 minder tot 271 minder)	⨁⨁⨁◯ Redelijk[a]	CRUCIAAL
Patient satisfaction - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL
Grade III or IV toxicities attributable to study drug												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	oral megestrol acetate	oral megestrol acetate plus olanzapine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	niet ernstig	niet gevonden	0/37 (0.0%)	0/39 (0.0%)	Niet te berekenen		⨁⨁⨁◯ Redelijk[a]	BELANGRIJK

Completion of chemotherapy - niet gerapporteerd

-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

Overall survival - niet gerapporteerd

-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

Progression-free survival - niet gerapporteerd

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	oral megestrol acetate	oral megestrol acetate plus olanzapine	Relatief (95% CI)	Absoluut (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1.1.1.10 Explanations

a. Navari 2010: unclear method of randomisation and allocation concealment, no blinding

Auteur(s): Brisbois, T.D., et al., Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Annals of Oncology, 2011. 22(9): p. 2086-2093.

Vraagstelling: THC versus placebo voor adult advanced cancer patients with poor appetite

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	THC	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Nausea score (ESAS)												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[b]	niet gevonden	Nausea scores were unaffected by THC treatment (p=0.532)				⨁◯◯◯ Zeer laag[a,b]	CRUCIAAL
Quality of life (FAACT): global, at 18 days												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[c]	niet gevonden	11	192899	-	SMD **0.33 lager** (0.92 lager tot 0.26 hoger)	⨁⨁◯◯ Laag[a,c]	CRUCIAAL
Patient satisfaction - niet gerapporteerd												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	THC	placebo	Relatief (95% CI)	Absoluut (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

Adverse events: nausea / vomiting

1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	5/11 (45.5%)	2/10 (20.0%)	**RR 2.27** (0.56 tot 9.20)	**254 meer per 1.000** (from 88 minder tot 1.000 meer)	⨁◯◯◯ Zeer laag[a,d]	BELANGRIJK

Adverse events: hives / rash

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	THC	placebo	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	3/11 (27.3%)	3/10 (30.0%)	**RR 0.91** (0.24 tot 3.51)	**27 minder per 1.000** (from 228 minder tot 753 meer)	⨁◯◯◯ Zeer laag[a,d]	BELANGRIJK

Adverse events: bowel obstruction/constipation

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	THC	placebo	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	0/11 (0.0%)	3/10 (30.0%)	**RR 0.13** (0.01 tot 2.26)	**261 minder per 1.000** (from 297 minder tot 378 meer)	⨁◯◯◯ Zeer laag[a,d]	BELANGRIJK

Completion of chemotherapy - niet gerapporteerd

-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

Overall survival - niet gerapporteerd

Certainty assessment							Aantal patiënten		Effect		Certainty	Important ie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	THC	placebo	Relatief (95% CI)	Absoluut (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

Progression-free survival - niet gerapporteerd

-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **SMD:** Standardised mean difference

1.1.1.11 Explanations

a. Brisbois 2011: unclear blinding of assessors, no ITT analysis

b. Only p-value reported, small sample size

c. CI around SMD includes -0.5

d. CI around RR includes 0.75 and 1.25

Onderzoeksvraag 4: Combinatie van medicatie bij de behandeling van patiënten met misselijkheid en braken die met anti-emiticum worden behandeld in de palliatieve fase

Vraag 4: Welke combinatie van medicatie is geschikt voor de behandeling van patiënten met misselijkheid en braken die met anti-emiticum worden behandeld in de palliatieve fase (inclusief thc/cannabis)?
Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Cox 2015	• Design: systematic review • Funding: none; CoI: none • Search date: Feb 2015 • Databases: Medline, CENTRAL, Embase, trial registries • Study designs: RCTs • N included studies: N=0 RCTs	• Eligibility criteria: adults (aged 18 years and over) receiving palliative care suffering from nausea or vomiting, or both • Exclusion: nausea or vomiting thought to be secondary to pregnancy or surgery; studies of levomepromazine for the control of nausea or vomiting associated with chemotherapy were excluded unless all the participants (or a specified subgroup, analysed separately) were receiving palliative care	Levomepromazine	-	• Duplicate selection • No language restriction
Davis 2010	• Design: systematic review • Funding: not reported; CoI: not reported • Search date: 2008 • Databases: PubMed, OVID Medline, CENTRAL, ProQuest	• Eligibility criteria: adults with active cancer, treatment for nausea and vomiting clinically determined to be related to the cancer or as a complication from the cancer	Antiemetics	• See below for results of included studies	• Limited to English language • Unclear if review process was done by independent reviewers • Quality appraisal using Jadad scale • Relevant included studies: Bruera 2004

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Study designs: RCTs, prospective trials, cohort studies, case series, single-case reports • N included studies: N=14 RCTs				
Dietz 2013	• Design: systematic review • Funding: unclear; CoI: none • Search date: Apr 2012 • Databases: Medline, Embase, The Cochrane Library, PsychInfo, Ovid Nursing • Study designs: RCTs, prospective trials, cohort studies, case series, case reports, systematic reviews • N included studies: N=0 RCTs	• Eligibility criteria: adults treated in the palliative care setting; pharmacological treatment of symptoms at the end of life with levomepromazine	Levomepromazine	-	• Limited to English language • Duplicate selection • Unclear if data extraction was done by independent reviewers
Doppen 2022	• Design: systematic review • Funding: none; CoI: none • Search date: Sep 2021 • Databases: PubMed, Embase, The Cochrane Library, clinicaltrials.gov • Study designs: all • N included studies: N=20 RCTs	• Eligibility criteria: primary research in children and/or adults prescribed medicinal cannabis product (plant-derived or synthetically manufactured), in any formulation or dose, for symptoms due to a terminal disease • Exclusion: study population was not clearly specified as	Medicinal cannabis	-	• Study selection, data extraction and quality appraisal done by independent reviewers • Restricted to English language • Relevant included RCTs: Stambaugh 1984

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		being “palliative”, “advanced”, “end-stage” or “incurable”; the medicinal cannabis was not prescribed			
Douglas 2009	• Design: systematic review • Funding: unclear; Col: unclear • Search date: May 2006 • Databases: Medline, Embase, Cinahl • Study designs: all • N included studies: N=0 RCTs	• Eligibility criteria: patients dying with chronic kidney disease • Exclusion: articles which did not relate to the management of symptoms in adult renal populations and those which described management of symptoms yet thought to be less relevant in the last days of life	Symptom management	-	• Unclear if review process was done by independent researchers • Unclear language restriction
Economos 2020	• Design: systematic review • Funding: King’s College London; Col: none • Search date: Jan 2019 • Databases: Medline, • Scopus, Web of Science, Central and EMBASE, trial registers • Study designs: all • N included studies: N=3 RCTs	• Eligibility criteria: patients diagnosed with cancer, excluding cancer survivors, with one or more of the following symptoms: depression, anxiety, sleep disorders, nausea, anorexia, weight loss, breathlessness, pain, constipation, fatigue and drowsiness	Mirtazapine	-	• Unclear if study selection was done by independent researchers • Data extraction and quality appraisal done by independent researchers • Restricted to English and French literature • No relevant included RCTs
Glare 2004	• Design: systematic review • Funding: Strategic Research Development grant	• Eligibility criteria: patients with cancer in an advanced stage and with nausea	Antiemetics	-	• Unclear if study selection was done by independent researchers

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	from NHMRC; CoI: unclear • Search date: June 2003 • Databases: US Clinical Guidelines Repository, Cochrane Library, Medline, Embase • Study designs: systematic reviews, RCT, phase I/II clinical trials, well-designed cohort/case-control studies and case series • N included studies: N=7 RCTs	• Exclusion: study objective was aimed at evaluating (a) antiemetics for the control of nausea and vomiting caused by emetogenic chemotherapy, or (b) agents for the treatment of bowel obstruction other than the standard antiemetics (such as surgery, tubes, or drugs intended to control secretions such as hyoscine or octreotide)			• Data extraction done by one researcher • Restricted to English literature • Quality appraisal with MERGE instrument • No relevant included studies
Miller 2014	• Design: systematic review • Funding: unclear; CoI: none • Search date: Oct 2012 • Databases: Medline, Cinahl • Study designs: any experimental design • N included studies: N=6 RCTs	• Eligibility criteria: anorexia in adult palliative care for malignant or nonmalignant, life-limiting conditions	Corticosteroids	• See below for results of included studies	• Study selection and quality appraisal done by independent reviewers • Unclear if data extraction was done by independent researchers • Evidence grading with SIGN system • Restricted to English literature • Relevant included studies: Bruera 2004
Mucke 2018	• Design: systematic review + meta-analysis	• Eligibility criteria: participants of any age, diagnosed with any advanced or end-stage	Cannabinoids	-	• Review process by independent reviewers • Language restriction unclear

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Funding: Commonwealth Department of Health, the NSW Government Centre for Medicinal Cannabis Research and Innovation, the Victorian Department of Health and Human Services and the Queensland Department of Health; NHMRC research fellowship #1041472; the Australian Government under the Substance Misuse Prevention and Service Improvements Grant Fund"; CoI: none • Search date: Mar 2017 • Databases: CENTRAL, Medline, PsycINFO, PubMed, and Scopus • Study designs: RCTs • N included studies: N=9 RCTs	medical disease (e.g. cancer, dementia, HIV/Acquired Immune Deficiency Syndrome (AIDS), heart disease, lung disease, and liver disease) • Exclusion: non-randomized studies, short abstracts, case reports, and studies without focus on palliative care aspects; studies on neuropathic pain in patients with HIV			• Complete GRADE process used • No relevant included RCTs
Murray-Brown 2015	• Design: systematic review • Funding: unclear; CoI: none • Search date: Nov 2014	• Eligibility criteria: adults receiving palliative care or suffering from an incurable progressive medical condition, and suffering	Haloperidol	-	• Duplicate selection • No language restriction • No relevant RCTs

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Databases: Medline, CENTRAL, Embase, Cinahl, AMED, trial registries • Study designs: RCTs • N included studies: N=1 RCTs	from nausea or vomiting, or both • Exclusion: nausea or vomiting, or both, thought to be secondary to pregnancy or surgery			
Sande 2019	• Design: systematic review • Funding: none; CoI: none • Search date: Nov 2017 • Databases: Medline, Embase • Study designs: RCTs • N included studies: N=15 RCTs	• Eligibility criteria: patients with cancer; at least 18 years of age; on opioids (weak or strong opioid) as defined by WHO's Analgesic Ladder for cancer pain relief; nausea and/or vomiting assessed as a primary or secondary outcome • Exclusion: nausea and vomiting related to chemotherapy, radiotherapy, malignant bowel obstruction, or postoperative settings	Management of opioid-induced nausea and vomiting	• See below for results of included studies	• Restricted to English literature • Unclear if study selection was done by independent reviewers • Data extraction and quality appraisal done by independent reviewers • GRADE process used • Relevant included studies: Bruera 2004
Solmi 2023	• Design: systematic review • Funding: none; CoI: extensive list in article • Search date: Feb 2022 • Databases: PubMed, PsychInfo, Embase, Cochrane Library • Study designs: meta-analyses	• Eligibility criteria: meta-analyses of observational studies (ie, case-control and cohort studies) and randomised controlled trials that reported on any outcome associated with cannabis and cannabinoids use in humans • Exclusion: systematic reviews without a meta-analysis, meta-analyses of	Cannabis	-	• Duplicate study selection and data extraction • No language restriction • Quality appraisal using Amstar instrument • No relevant included studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• N included studies: N=0 RCTs	risk factors for cannabinoids use, meta-analyses of cross-sectional studies only, pooled analyses of studies identified without a systematic search, and individual studies			
Storrar 2014	• Design: systematic review • Funding: Cochrane Collaboration; CoI: none • Search date: Nov 2013 • Databases: Medline, Embase, CENTRAL, AMED, Cinahl, trial registers • Study designs: RCTs • N included studies: N=0 RCTs	• Eligibility criteria: adults receiving palliative care or suffering from an incurable progressive medical condition, and suffering from nausea or vomiting, or both • Exclusion: nausea or vomiting, or both, thought to be secondary to pregnancy or surgery; antiemetic(s) used for the prophylaxis of nausea or vomiting associated with chemotherapy	Droperidol	-	• Duplicate selection • No language restriction
Sutherland 2018	• Design: systematic review • Funding: Health Education Thames Valley; CoI: none • Search date: Sep 2017 • Databases: CENTRAL, Medline, Embase • Study designs: RCTs • N included studies: N=14 RCTs	• Eligibility criteria: patients with cancer (of any type or stage), who had nausea and vomiting treated with olanzapine, or where olanzapine was used to prevent nausea and vomiting • Exclusion: studies in which olanzapine was used for the treatment or prevention of nausea and vomiting in non-cancer patients	Olanzapine	• See below for results of included studies	• Review process by independent reviewers • No language restriction • Relevant included RCTs: Navari 2013

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Tramer 1999	• Design: systematic review • Funding: PROSPER research grant from the Swiss National Science Foundation (Grant No 3233–051939.97); CoI: unclear • Search date: Apr 1998 • Databases: Medline, Embase, Cochrane Library • Study designs: RCTs • N included studies: N=14 RCTs	• Eligibility criteria: prophylactic efficacy of antiemetic interventions compared with placebo or no treatment in patients with acute, postoperative pain treated with a PCA device containing an opioid • Exclusion: abstracts, letters, and review articles; interventions to treat established postoperative nausea and vomiting	Prophylactic antiemetics during patient-controlled analgesia therapy	-	• Unclear if study selection was done by independent reviewers • Data extraction and quality appraisal done by independent reviewers • No language restriction • Quality appraisal using Jadad scale • No relevant included studies
Vayne-Bossert 2017	• Design: systematic review • Funding: Mater Research - The University of Queensland, School of Pharmacy and Menzies Health Institute Queensland, GriFith University, The Mater Palliative Care Research Fund and St Vincent's Hospital Brisbane, Australia; CoI: none • Search date: Aug 2016 • Databases: CENTRAL, Medline, Embase, Cinahl, EBSCO, Web	• Eligibility criteria: participants with cancer suffering from nausea, vomiting or both not related to chemotherapy, radiotherapy, or surgery, aged 18 years and above	Corticosteroids	• See below for results of included studies	• Review process by independent reviewers • No language restriction • Relevant included studies: Bruera 2004

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	of Science, LILACS, Conference Proceedings Citation Index, trial registries • Study designs: RCTs • N included studies: N=3 RCTs				

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality

Bruera 2004	• Design: RCT
	• Funding: Brown Foundation, Houston, Texas; CoI: not reported
	• Setting: 5 international centres
	• Sample size: N=51
	• Duration: 7 days
		• Eligibility criteria: patients with a history of chronic nausea (defined as nausea lasting more than 2 weeks) resulting from advanced cancer (local recurrence or metastatic disease); had residual mild to moderate nausea (greater than or equal to 3 on a 0-10 numerical scale measuring intensity of nausea) despite treatment with metoclopramide at a minimal daily dose of 40-60 mg for 2 days; had no evidence of mechanical bowel obstruction; had received no chemotherapy or radiation therapy for 4 weeks; had a normal cognitive status (defined as normal state of arousal	Dexamethasone, 10 mg orally twice a day (N=25)
			
			vs.
			
			Placebo (N=26)
				CRITICAL OUTCOMES
				
				• Nausea / vomiting: NRS
				  ○ Intensity of nausea: mean change from baseline (SD)
				  ▪ Day 3: 4.5 (4.1) vs. 2.9 (3.9), p=0.16
				  ▪ Day 8: 5.9 (3.6) vs. 5.7 (3.2), p=0.85
				  ○ Median number of daily vomiting episodes: 0 at day 3 and 8 in both groups (NS)
				• Quality of life: FACT, day 8, mean (SD)
				  ○ Physical well-being: 17.5 (5.9) vs. 17.9 (6.6)
				  ○ Social / Family well-being: 18.2 (5.8) vs. 19.6 (7.4)
				  ○ Emotional well-being: 13.7 (5.9) vs. 13.1 (5.3)
				  ○ Functional well-being: 10.9 (5.8) vs. 12.3 (7.0)
				• Patient satisfaction: not reported
				• Adverse events: 6 vs.8
				  ○ Ankle edema: 8% vs. 12%
				  ○ Insomnia: 4% vs. 8%
					Level of evidence: unclear risk of bias
					
					• Each participating pharmacy randomly assigned patients: not reported how
					• Capsules containing both drugs were identical in appearance
					• Double-blind study, but unclear if assessors were blinded
					• Unclear if ITT analysis was used, 3 vs. 5 drop-outs

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		and absence of obvious clinical findings of confusion, memory or concentration deficit); and were 16 years of age or older • Exclusion criteria: had already received dexamethasone within the previous 4 weeks; had been treated with antiemetics other than metoclopramide during the preceding 3 days; did not have a stable opioid dose (defined as a dose change of less than 50% in the past 3 days); or had contraindications (i.e., diabetes mellitus) to oral dexamethasone therapy • *A priori* patient characteristics: ○ Median age: 66 vs. 60y ○ M/F: 10/15 vs. 14/12/1? ○ Cancer type: gastrointestinal N=22, gynaecological N=7, genitourinary N=6, lung N=3, breast N=2, unknown N=9		○ Restlessness: 4% vs. 8% ○ Other mild side effects: 8% vs. 4%	
Johansson 1982	• Design: cross-over RCT • Funding: not reported; CoI: not reported	• Eligibility criteria: adult patients with an age range of 18-70 years, with a good performance status (less than 2 on the EGOG scale),	Nabilone 2 mg twice daily orally (N=26) vs.	CRITICAL OUTCOMES • Nausea / vomiting:	Level of evidence: high risk of bias • The order of administration of the

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Setting: unclear • Sample size: N=27 • Duration: recruitment Sep 1981 – Apr 1982	receiving the same cycles of cancer chemotherapy as previously, who had uncontrolled nausea and vomiting despite the use of standard antiemetic drugs • Exclusion criteria: patients with known psychotic or cardiovascular diseases, currently under medication, i.e. with phenothiazines, or with previous usage of marijuana • *A priori* patient characteristics: ○ Cancer type: ovarian N=13, cervix N=2, fallopian tubes N=2, testis N=2	Prochlorperazine 10 mg twice daily orally (N=23)	○ Severity of nausea (none-mild-moderate-severe): less with nabilone (p=0.027) ▪ None: 17% vs. 0% ▪ Mild: 33% vs. 17% ▪ Moderate: 39% vs. 61% ▪ Severe: 11% vs. 22% ○ Less nausea: 9/18 vs. 1/18 ○ Mean number of vomiting episodes: 18.4 vs. 38.7, p<0.001 ○ Proportion without vomiting: 3 vs. 0 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: ○ At least one adverse event: 14/26 vs. 9/23	drugs was randomly allocated, but unclear how • Double-blind study, but unclear if assessors were blinded • No ITT analysis, only 18 patients included in efficacy analysis
McCabe 1988	• Design: cross-over RCT • Funding: not reported; CoI: not reported • Setting: single cancer centre, US • Sample size: N=36 • Duration: unclear	• Eligibility criteria: adult patients undergoing chemotherapeutic treatment, no prior history of psychiatric illness or preexisting cardiac disease; performance status 0-1; severe nausea and vomiting that was refractory to standard antiemetics • *A priori* patient characteristics: ○ Median age: 48y ○ M/F: 9/27 ○ Cancer type: breast N=11, hematologic N=9,	Delta-9-tetrahydrocannabinol 15 mg/m^2 (N=36) vs. Prochlorperazine 10 mg/day (N=36)	CRITICAL OUTCOMES • Nausea / vomiting: ○ Complete response: 9 vs. 0 ○ Partial response: 14 vs. 1 ○ No response: 13 vs. 35 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported	Level of evidence: unclear risk of bias • The patient served as his own control, and received each study drug twice in a randomly allocated sequence (method unclear) • Blinding unclear (but unlikely: prochlorperazine was supplied in its usual tablet form) • Nausea was rated on a 0-4 scale: 0 = None; 1 = Mild; 2= Moderate; 3=

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		sarcoma N=6, gastrointestinal N=5			Severe; 4= Incapacitating • Complete response was defined as the complete absence of nausea and vomiting; partial response represented at least a 50% decrease in frequency and intensity of nausea and vomiting as compared to baseline; no response was defined as less than a 50% decrease in nausea and vomiting
Navari 2013	• Design: RCT • Funding: supported by the Reich Family Endowment for the Care of the Whole Patient; CoI: none • Setting: 3 outpatient oncology centers • Sample size: N=276 • Duration: 72h observation period	• Eligibility criteria: adult patients with histologically or cytologically confirmed malignant disease that were chemotherapy naive and scheduled to receive HEC (cisplatin, ≥70 mg/m^2; cyclophosphamide, ≥600–1000 mg/m^2; and doxorubicin, ≥50–60 mg/m^2); without nausea in 24 h prior to beginning of chemotherapy and should have serum creatinine of ≤2.0 mg/dl, serum bilirubin of ≤2.0 mg/dl, SGOT or SGPT values of ≤3 times the upper limits of normal, and absolute neutrophil count of ≥1500 mm^3; patients of childbearing potential	Olanzapine 10 mg orally every 24h for 72h (+ oral placebo twice in every 24-h period for 72h) (N=58) vs. Metoclopramide 10 mg orally every 8h for 72h (N=54)	CRITICAL OUTCOMES • Nausea / vomiting: ○ No emesis during 72h observation period: 39/56 vs. 15/52, p<0.01 ○ No nausea during 72h observation period: 38/56 vs. 12/52, p<0.01 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: ○ No grade 3 or 4 toxicities attributable to the study drugs in any of the patients for the treatment periods	Level of evidence: unclear risk of bias • Computer-generated random assignment schedule created by a statistician not involved with the study • Treatment packages were identical with neither the patients nor the investigators knowing which treatment the patients were assigned • Only patients with CINV (N=112) received the study medication; 4/112 were excluded from analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		(men and women) must consent to use adequate contraception throughout protocol therapy; women of childbearing potential must have a negative urine pregnancy test; patients should have no severe cognitive compromise, no known history of CNS disease (e.g., brain metastases, seizure disorder), no treatment with other antipsychotic agents such as risperidone, quetiapine, clozapine, phenothiazine or butyrophenone for 30 days prior to or during protocol therapy; patients on chronic phenothiazine administration as an antipsychotic agent was not allowed, but they may receive prochlorperazine and other phenothiazines as rescue antiemetic therapy; patients should have no concurrent use of ethyol, no concurrent abdominal radiotherapy, no concurrent use of quinolone antibiotic therapy, no chronic alcoholism (as determined by the investigator), no			

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		known hypersensitivity to olanzapine, no known cardiac arrhythmia, uncontrolled congestive heart failure, or acute myocardial infarction within the previous 6 months, and no history of uncontrolled diabetes mellitus. • *A priori* patient characteristics: ○ Median age: 61 vs. 63y ○ M/F: 28/28 vs. 30/22 ○ Cancer type: breast N=54, NSCLC N=37, lymphoma N=10, bladder N=7			
Sallan 1975	• Design: cross-over RCT • Funding: grants (CA 19589, CA 22719, and CA 17979) from the National Institutes of Health; CoI: not reported • Setting: unclear • Sample size: N=84 • Duration: unclear	• Eligibility criteria: patients with neoplasms receiving chemotherapy, nausea and vomiting were inadequately controlled by conventional antiemetics, including phenothiazines • Exclusion criteria: pregnant women and patients with a history of emotional instability or untoward reactions to psychoactive drugs • *A priori* patient characteristics: ○ Mean age: 32.5y ○ M/F: 51/33	Delta-9-tetrahydrocannabinol 10 mg/m^2 (N=84) vs. Prochlorperazine 10 mg/day (N=84)	CRITICAL OUTCOMES • Nausea / vomiting: ○ Complete response: 36/79 vs. 16/78 treatment courses ○ Partial response: 10/79 vs. 15/78 ○ No response: 33/79 vs. 47/78 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported	Level of evidence: high risk of bias • Method of randomization and allocation concealment unclear • Double-blinded; identical opaque capsules; assessors were also blinded • 27 patients received only one course of study drug and were removed from the study • Complete response was defined as no nausea or vomiting after chemotherapy; partial response = a reduction

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
					in the severity of nausea and vomiting; no response = no reduction in the severity of nausea and vomiting
Stambaugh 1984	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single private practice, US • Sample size: N=20 • Duration: 6 months recruitment period	• Eligibility criteria: patients with persistent nausea and vomiting from cancer chemotherapy determined to be refractory to maximally recommended doses of conventional antiemetics • Exclusion criteria: subjects with severe liver or renal disease or with CNS metastasis • *A priori* patient characteristics: ○ Not reported	Levonantradol IM 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg (N=16) vs. Placebo (N=4)	CRITICAL OUTCOMES • Nausea / vomiting: ○ Complete response: the antiemetic response of levonantradol for each of the doses were significantly different from those of placebo ($p<0.05$), but there was no difference between doses • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: ○ Eight of the 16 subjects who received 0.5 to 2.0 mg levonantradol experienced more than one side effect and did not receive all four dosings because of toxicity ○ No subject receiving placebo was discontinued due to toxicity	Level of evidence: unclear risk of bias • Random design using a Latin-square treatment sequence; method unclear • Double-blinded, but unclear if assessors were blinded • Unclear how many patients were included in analysis • Complete response was defined as the complete absence of nausea and vomiting; partial response represented a 50% reduction in nausea and vomiting compared to prior treatment and less than five episodes of emesis during the evaluation; no response was defined as less than a 50% reduction in the incidence of nausea and vomiting compared to prior treatments and five or more episodes of

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
					emesis in the 24-hour observation period

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; ITT: intention to treat; IV: intravenous; NRS: numeric rating scale; NS: not significant; PCA: patient-controlled analgesia; RCT: randomised controlled trial; SD: standard deviation.

References

Bruera, E., et al., Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. Journal of Pain & Symptom Management, 2004. 28(4): p. 381-8.

Cox, L., E. Darvill, and S. Dorman, Levomepromazine for nausea and vomiting in palliative care. Cochrane Database of Systematic Reviews, 2015(11): p. CD009420.

Davis M, Hallerberg G. A systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy of radiation. Journal of Pain and Symptom Management 2010;39(4):756-67.

Dietz, I., et al., Evidence for the use of Levomepromazine for symptom control in the palliative care setting: A systematic review. BMC Palliative Care, 2013. 12(1).

Doppen, M., et al., Cannabis in Palliative Care: A Systematic Review of Current Evidence. Journal of Pain & Symptom Management, 2022. 64(5): p. e260-e284.

Douglas, C., et al., Symptom management for the adult patient dying with advanced chronic kidney disease: a review of the literature and development of evidence-based guidelines by a United Kingdom Expert Consensus Group. Palliative Medicine, 2009. 23(2): p. 103-10.

Economos, G., et al., What is the evidence for mirtazapine in treating cancer-related symptomatology? A systematic review. Supportive Care in Cancer, 2020. 28(4): p. 1597-1606.

Glare, P., et al., Systematic review of the efficacy of antiemetics in the treatment of nausea in patients with far-advanced cancer. Supportive Care in Cancer, 2004. 12(6): p. 432-40.

Hardy, J., et al., A randomized open-label study of guideline-driven antiemetic therapy versus single agent antiemetic therapy in patients with advanced cancer and nausea not related to anticancer treatment. BMC Cancer, 2018. 18(1): p. 510.

Hardy, J.R., et al., Methotrimeprazine versus haloperidol in palliative care patients with cancer-related nausea: a randomised, double-blind controlled trial. BMJ Open, 2019. 9(9): p. e029942.

Johansson R, Kilkku P, Groenroos M. A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy. Cancer Treatment Reviews 1982;9(Suppl B):25-33.

McCabe M, Smith FP, Macdonald JS, Woolley PV, Goldberg D, Schein PS. Efficacy of tetrahydrocannabinol in patients refractory to standard antiemetic therapy. Investigational New Drugs 1988;6(3):243-6.

Miller, S., et al., Use of corticosteroids for anorexia in palliative medicine: A systematic review. Journal of Palliative Medicine, 2014. 17(4): p. 482-485.

Mucke, M., et al., Systematic review and meta-analysis of cannabinoids in palliative medicine. Journal of Cachexia, Sarcopenia and Muscle, 2018. 9(2): p. 220-234.

Murray-Brown, F. and S. Dorman, Haloperidol for the treatment of nausea and vomiting in palliative care patients. Cochrane Database of Systematic Reviews, 2015(11): p. CD006271.

Navari R, Nagy C, Gray S. The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Supportive Care in Cancer 2013; Vol. 21, issue 6:1655-63.

Sallan SE, Zinberg NE, Frei E. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. New England Journal of Medicine 1975;293:795-7.

Sande, T.A., B.J.A. Laird, and M.T. Fallon, The Management of Opioid-Induced Nausea and Vomiting in Patients with Cancer: A Systematic Review. Journal of Palliative Medicine, 2019. 22(1): p. 90-97.

Solmi, M., et al., Balancing risks and benefits of cannabis use: umbrella review of meta-analyses of randomised controlled trials and observational studies. BMJ, 2023. 382: p. e072348.

Stambaugh JE, McAdams J, Vreeland F. Dose ranging evaluation of the antiemetic efficacy and toxicity of intramuscular levonantradol in cancer subjects with chemotherapyinduced emesis. J Clin Pharmacol 1984;24:480–485.

Storrar, J., et al., Droperidol for treatment of nausea and vomiting in palliative care patients. Cochrane Database of Systematic Reviews, 2014(11): p. CD006938.

Sutherland, A., et al., Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults. Cochrane Database of Systematic Reviews, 2018. 9: p. CD012555.

Tramer MR, Walder B. Efficacy and adverse effects of prophylactic antiemetics during patient-controlled analgesia therapy: a quantitative systematic review. Anesthesia and Analgesia 1999;88:1354-61.

Vayne-Bossert, P., et al., Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery). Cochrane Database of Systematic Reviews, 2017. 7: p. CD012002.

GRADE-profielen

Auteur(s): Bruera, E., et al., Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. Journal of Pain & Symptom Management, 2004. 28(4): p. 381-8.

Vraagstelling: Dexamethason versus placebo voor patients with advanced cancer and refractory nausea

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	dexamethason	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Intensity of nausea (NRS): mean change from baseline at day 3												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[b]	niet gevonden	22	21	-	SMD **0.39 hoger** (0.21 lager tot 1 hoger)	⨁⨁◯◯ Laag[a,b]	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	dexamethason	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Intensity of nausea (NRS): mean change from baseline at day 8												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[c]	niet gevonden	22	21	-	SMD **0.06 hoger** (0.54 lager tot 0.66 hoger)	⨁⨁◯◯ Laag[a,c]	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	dexamethason	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Median number of daily vomiting episodes												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[d]	niet gevonden	0	0	-	MD **0** (0 tot 0)	⨁◯◯◯ Zeer laag[a,d]	CRUCIAAL
Quality of life: FACT at day 8, Physical well-being												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	dexamethason	placebo	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[c]	niet gevonden	22	21	-	SMD **0.06 lager** (0.66 lager tot 0.54 hoger)	⨁◯◯◯ Zeer laag[a,c]	CRUCIAAL

Quality of life: FACT at day 8, Social / Family well-being

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	dexamethason	placebo	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[e]	niet gevonden	22	21	-	SMD **0.21 lager** (0.81 lager tot 0.39 hoger)	⨁⨁◯◯ Laag[a,e]	CRUCIAAL

Quality of life: FACT at day 8, Emotional well-being

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	dexamethason	placebo	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[b]	niet gevonden	22	21	-	SMD **0.1 hoger** (0.49 lager tot 0.7 hoger)	⨁⨁◯◯ Laag[a,b]	CRUCIAAL

Quality of life: FACT at day 8, Functional well-being

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	dexamethason	placebo	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[e]	niet gevonden	22	21	-	SMD **0.21 lager** (0.81 lager tot 0.39 hoger)	⨁⨁◯◯ Laag[a,e]	CRUCIAAL
Patient satisfaction - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	dexamethason	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Proportion of patients with at least one adverse event												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[f]	niet gevonden	6/22 (27.3%)	8/21 (38.1%)	**RR 0.72** (0.30 tot 1.71)	**107 minder per 1.000** (from 267 minder tot 270 meer)	⨁◯◯◯ Zeer laag[a,f]	BELANGRIJK

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	dexamethason	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Chemotherapy completion - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK
Overall survival - niet gerapporteerd												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	dexamethason	placebo	Relatief (95% CI)	Absoluut (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

Progression-free survival - niet gerapporteerd

-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **SMD:** Standardised mean difference

1.1.1.12 Explanations

a. Bruera 2004: unclear method of randomisation and allocation concealment, unclear blinding of assessors, unclear ITT analysis (probably not)

b. CI around SMD includes 0.5

c. CI around SMD includes -0.5 and 0.5

d. No data to calculate precision

e. CI around SMD includes -0.5

f. CI around RR includes 0.75 and 1.25

Auteur(s): Stambaugh JE, McAdams J, Vreeland F. Dose ranging evaluation of the antiemetic efficacy and toxicity of intramuscular levonantradol in cancer subjects with chemotherapyinduced emesis. J Clin Pharmacol 1984;24:480–485.

Vraagstelling: Levonantradol versus placebo voor refractory CINV

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	levonantradol	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Complete response (absence of nausea and vomiting)												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	levonantradol	placebo	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[b]	niet gevonden	The antiemetic response of levonantradol for each of the doses were significantly different from those of placebo ($p<0.05$), but there was no difference between doses				⨁◯◯◯ Zeer laag[a,b]	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	levonantradol	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Quality of life - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL
Patient satisfaction - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	levonantradol	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Adverse events												

1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[b]	niet gevonden	- Eight of the 16 subjects who received 0.5 to 2.0 mg levonantradol experienced more than one side effect and did not receive all four dosings because of toxicity - No subject receiving placebo was discontinue				⨁◯◯◯ Zeer laag[a,b]	BELANGRIJK

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	levonantradol	placebo	Relatief (95% CI)	Absoluut (95% CI)		
							d due to toxicity					
Completion of chemotherapy - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	levonantradol	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Overall survival - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK
Progression-free survival - niet gerapporteerd												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	levonantradol	placebo	Relatief (95% CI)	Absoluut (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

CI: Confidence interval

1.1.1.13 Explanations

a. Stambaugh 1984: poor describing of methodology

b. Insufficient information to calculate precision, small sample size

Auteur(s): Johansson R, Kilkku P, Groenroos M. A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy. Cancer Treatment Reviews 1982;9(Suppl B):25-33.

Vraagstelling: Nabilone versus prochlorperazine voor refractory CINV

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	nabilone	prochlorperazine	Relatief (95% CI)	Absoluut (95% CI)		
Proportion of patients without nausea												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[b]	niet gevonden	3/18 (16.7%)	0/18 (0.0%)	**RR 7.00** (0.39 tot 126.48)	**0 minder per 1.000** (from 0 minder tot 0 minder)	⨁◯◯◯ Zeer laag[a,b]	CRUCIAAL
Proportion of patients with less nausea												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	nabilone	prochlorperazine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	niet ernstig	niet gevonden	9/18 (50.0%)	1/18 (5.6%)	**RR 9.00** (1.27 tot 63.89)	**444 meer per 1.000** (from 15 meer tot 1.000 meer)	⨁⨁⨁◯ Redelijk[a]	CRUCIAAL

Mean number of vomiting episodes

1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	ernstig[c]	niet gevonden	18.4 vs. 38.7, p<0.001				⨁⨁◯◯ Laag[a,c]	CRUCIAAL

Proportion of patients without vomiting

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	nabilone	prochlorperazine	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[b]	niet gevonden	3/18 (16.7%)	0/18 (0.0%)	**RR 7.00** (0.39 tot 126.48)	**0 minder per 1.000** (from 0 minder tot 0 minder)	⨁◯◯◯ Zeer laag[a,b]	CRUCIAAL
Quality of life - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL
Patient satisfaction - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	nabilone	prochlorperazine	Relatief (95% CI)	Absoluut (95% CI)		
Proportion of patients with at least 1 adverse event												
1	gerandomiseerde trials	ernstig[a]	niet ernstig	niet ernstig	zeer ernstig[b]	niet gevonden	14/26 (53.8%)	9/23 (39.1%)	**RR 1.38** (0.74 tot 2.56)	**149 meer per 1.000** (from 102 minder tot 610 meer)	⨁◯◯◯ Zeer laag[a,b]	BELANGRIJK
Chemotherapy completion - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK
Overall survival - niet gerapporteerd												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	nabilone	prochlorperazine	Relatief (95% CI)	Absolut (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

Progression-free survival - niet gerapporteerd

-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1.1.1.14 Explanations

a. Johansson 1982: unclear method of randomisation and allocation concealment, unclear blinding of assessors, no ITT analysis

b. CI around RR includes 0.75 and 1.25

c. Optimal information size probably met, but insufficient data to calculate

Auteur(s): Navari R, Nagy C, Gray S. The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Supportive Care in Cancer 2013; Vol. 21, issue 6:1655-63.

Vraagstelling: Olanzapine versus metoclopramide voor refractory CINV

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	olanzapine	metoclopramide	Relatief (95% CI)	Absoluut (95% CI)		
No emesis during 72h observation period												
1	gerandomiseerde trials	niet ernstig	niet ernstig	niet ernstig	niet ernstig	niet gevonden	39/56 (69.6%)	15/52 (28.8%)	**RR 2.41** (1.52 tot 3.83)	**407 meer per 1.000** (from 150 meer tot 816 meer)	⨁⨁⨁⨁ Hoog	CRUCIAAL
No nausea during 72h observation period												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	**Studieopzet**	**Risk of bias**	**Inconsistentie**	**Indirect bewijs**	**Onnauwkeurigheid**	**Andere factoren**	**olanzapine**	**metoclopramide**	**Relatief (95% CI)**	**Absoluut (95% CI)**		
1	gerandomiseerde trials	niet ernstig	niet ernstig	niet ernstig	niet ernstig	niet gevonden	38/56 (67.9%)	12/52 (23.1%)	**RR 2.94** (1.73 tot 4.99)	**448 meer per 1.000** (from 168 meer tot 921 meer)	⨁⨁⨁⨁ Hoog	CRUCIAAL
Quality of life - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL
Patient satisfaction - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	olanzapine	metoclopramide	Relatief (95% CI)	Absoluut (95% CI)		
Grade 3 or 4 toxicities attributable study drug												
1	gerandomiseerde trials	niet ernstig	niet ernstig	niet ernstig	niet ernstig	niet gevonden	0/56 (0.0%)	0/52 (0.0%)	Niet te berekenen		⨁⨁⨁⨁ Hoog	BELANGRIJK
Completion of chemotherapy - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK
Overall survival - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK
Progression-free survival - niet gerapporteerd												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	olanzapine	metoclopramide	Relatief (95% CI)	Absoluut (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

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

Auteur(s):

Vraagstelling: THC versus prochlorperazine voor refractory CINV

Setting:

Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	THC	prochlorperazine	Relatief (95% CI)	Absoluut (95% CI)		
Proportion of patients with complete response (nausea and vomiting)												
2	gerandomiseerde trials	ernstig [a,b]	niet ernstig	niet ernstig	niet ernstig	niet gevonden	45/115 (39.1%)	16/114 (14.0%)	**RR 2.73** (1.67 tot 4.45)	**243 meer per 1.000** (from 94 meer tot 484 meer)	⨁⨁⨁◯ Redelijk [a,b]	CRUCIAAL
Proportion of patients without response (nausea and vomiting)												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	THC	prochlorperazine	Relatief (95% CI)	Absoluut (95% CI)		
2	gerandomiseerde trials	ernstig[a,b]	ernstig[c]	niet ernstig	niet ernstig	niet gevonden	46/115 (40.0 %)	82/114 (71.9%)	**RR 0.56** (0.43 tot 0.72)	**316 minder per 1.000** (from 410 minder tot 201 minder)	⨁⨁◯◯ Laag[a,b,c]	CRUCIAAL
Quality of life - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL
Patient satisfaction - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	THC	prochlorperazine	Relatief (95% CI)	Absoluut (95% CI)		
Adverse events - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK
Completion of chemotherapy - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK
Overall survival - niet gerapporteerd												
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK
Progression-free survival - niet gerapporteerd												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	THC	prochlorperazine	Relatief (95% CI)	Absoluut (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	BELANGRIJK

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

1.1.1.15 Explanations

a. McCabe 1988: unclear method of randomisation and allocation concealment, unclear blinding

b. Sallan 1975: unclear method of randomisation and allocation concealment, no ITT analysis, analysis not at patient level

c. I2 80%, different definition of no response