

Somatostatin analogues compared to placebo and other pharmacological agents in the management of symptoms of inoperable malignant bowel obstruction: a systematic review

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Abstract

Context. Somatostatin analogues are commonly used to relieve symptoms in malignant bowel obstruction (MBO) but are more expensive than other anti-secretory agents.

Objective. To evaluate the evidence of effectiveness of somatostatin analogues compared to placebo and/or other pharmacological agents in relieving vomiting in patients with inoperable MBO.

Method. MEDLINE, EMBASE, CINAHL, The Cochrane Controlled Trials Register databases were systematically searched; reference lists of relevant articles were hand-searched. Cochrane risk of bias tool was used.

Results. The search identified 420 unique studies. Seven randomised controlled trials (RCTs) met the inclusion criteria (six octreotide studies; one lanreotide); 220 people administered somatostatin analogues and 207 placebo or hyoscine butylbromide. Three RCTs compared a somatostatin analogue with placebo and four with hyoscine butylbromide. Two adequately powered multicentre RCTs with a low Cochrane risk of bias reported no significant difference between somatostatin analogues and placebo in their primary endpoints. Four RCTs with a high/unclear Cochrane risk of bias reported that somatostatin analogues were more effective than hyoscine butylbromide in reducing vomiting.

Conclusion. There is low-level evidence of benefit with somatostatin analogues in the symptomatic treatment of MBO. However, high level evidence from trials with low risk of bias found no benefit of somatostatin analogues for their primary outcome. There is debate regarding the clinically relevant study endpoint for symptom control in MBO and when it should be measured. The role of somatostatin analogues in this clinical situation requires further adequately powered, well designed trials with agreed clinically important endpoints and measures.

Key words

Inoperable malignant bowel obstruction, palliative care, somatostatin analogues, octreotide, randomised controlled trial, vomiting

Running title

Somatostatin analogues in inoperable malignant bowel obstruction review

1. Introduction

Malignant bowel obstruction (MBO) is a complication of abdominal and pelvic malignancies. (1, 2, 3) It is reported to occur in 10% to 50% of patients with ovarian cancer and up to 15% of patients with gastrointestinal cancers. (1, 4) The International Conference on MBO and Clinical Protocol Committee proposed the following specific definition criteria for MBO: “(a) Clinical evidence of bowel obstruction, (b) Bowel obstruction beyond the Ligament of Treitz, (c) Intra-abdominal primary cancer with incurable disease and (d) Non-intra-abdominal primary cancer with clear intra-peritoneal disease”. (5)

In MBO, mechanical obstruction occurs due to internal or external gastrointestinal (GI) tract malignancy, or functional occlusion from infiltration of bowel muscle or GI nerves by tumour thus preventing transit of food and fluids through the GI tract. (1) As a consequence unabsorbed secretions and oral intake accumulate in the GI tract and cause symptoms associated with MBO. These include nausea, vomiting, pain, abdominal distension and constipation. (6 - 11)

Management of MBO depends on the location of obstruction, the goals of treatment and the prognosis. (1) When appropriate, surgical intervention including bowel resection, stoma formation or endoscopic stenting is offered in the first instance. (12) When surgical approaches are not appropriate, symptom-directed treatment aimed at reducing symptoms of MBO and optimising quality of life becomes the main priority. (13, 30) This may include nasogastric tube or venting gastrostomy insertion; or medications to reduce GI secretions, emesis and pain.

Several studies have reported that dexamethasone, prednisolone, hyoscine butylbromide (scopolamine butylbromide), somatostatin analogues and chlorpromazine can be effective in relieving the symptoms of MBO, with the main outcomes being control of nausea, vomiting, pain or resolution of obstruction. (14-18) Palliative care guidelines often recommend the use of metoclopramide as a prokinetic agent in partial MBO (without colicky pain) or hyoscine butylbromide and/or somatostatin analogues as anti-secretory/ anti-spasmodic agents in complete MBO. (19, 20, 54, 55, 56)

The most commonly used somatostatin analogue is octreotide, first developed in 1979. Lanreotide and pasireotide are alternatives. Somatostatin analogues have similar physiological activity to the natural hormone somatostatin. Their mechanism of action includes splanchnic blood vessel vasoconstriction; reduction of secretions by the intestine and pancreas; increased GI absorption of water and electrolytes; and changes in bowel transit. (6, 21)

As somatostatin analogues are more expensive than other anti-secretory agents used in MBO, (17) and to help clinicians make appropriate treatment decisions, it is important that the effectiveness of octreotide as compared to other pharmacological agents is determined. There are currently no systematic reviews evaluating the effectiveness of somatostatin analogues with placebo or other pharmacological agents in MBO. (9, 22 - 25)

The objective of this systematic review is to evaluate the evidence of effectiveness for somatostatin analogues as compared to placebo, and other pharmacological agents in reduction of vomiting as a primary outcome and reduction of pain and abdominal distension as secondary outcomes in patients with inoperative MBO. The review will also report on systematically collected side effects of somatostatin analogues.

2. Methods

This systematic review was conducted and reported in accordance with an *a priori* protocol which conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) 2015 guidelines, (26, 68) and was prospectively registered with International Prospective Register of Systematic Reviews (PROSPERO) on 2nd May 2015; registration number: CRD42015020207.

2.1 Search strategy

A comprehensive search of different electronic databases using a combination of medical subheadings (MeSH) terms and free text was carried out to identify potential studies for inclusion in the review. The retrieval started from 1979, when somatostatin analogues were first clinically used, to August 2015 (the search date). The following databases were searched: MEDLINE, EMBASE, CINAHL and The Cochrane Controlled Trials Register. Other sources such as the registers of controlled trials in progress and conference proceedings were also searched. Reference lists of relevant articles were hand searched. The MEDLINE search strategy (table 1) was adapted to other databases.

Table 1. Search strategy in Medline

No.	Query
#1	(octreotide or lanreotide or pasireotide).mp
#2	Sandostatin*.mp.
#3	("201995" or 201-995 or RWM8CCW8GP or "83150769" or 83150-76-9).mp.
#4	#1 or #2 or #3
#5	exp intestinal obstruction/
#6	((intestin* or bowel*) adj3 (obstruct* or block*)).mp.
#7	#5 or #6
#8	exp neoplasm/
#9	(neoplasm* or tumo?r* or cancer* or malignan*).mp.
#10	#8 or #9
#11	#4 and #7 and #10

2.2 Eligibility and selection criteria

Inclusion criteria: (a) Randomised controlled trials and quasi-randomised controlled trials that compared somatostatin analogues with placebo and/or other pharmacological agents; consecutive cohort studies were included for toxicity reporting over baseline where toxicity was systematically collected prospectively; (b) adults, aged 18 years and over, with inoperable MBO; (c) evaluated change in symptoms of inoperable MBO; (d) no study setting, language or publication status restrictions were imposed.

Exclusion criteria: Studies that compared somatostatin analogues with decompression of the gut by surgery, nasogastric tube (NGT), venting gastrostomy, or stenting.

Two reviewers (GPO & EGB) independently performed eligibility assessment of identified studies using the inclusion and exclusion criteria. Full papers were retrieved for those fulfilling the criteria, and for publications for which eligibility could not be assessed on the basis of the titles and abstracts alone. These two reviewers then assessed the full text of all potentially relevant studies. Disagreements or discrepancies at all stages were resolved by consensus and with recourse to a third reviewer (JWB), if necessary. The reasons for excluding a full text study are shown in the PRISMA flow chart (Figure 1).

2.3 Data extraction, assessment and analysis

Two reviewers (GPO and EGB), independently extracted data from the included studies. Participants' characteristics, interventions, controls and outcomes were extracted from the included studies. Discrepancies were resolved through discussions with a third reviewer (JWB).

2.4 Risk of bias in individual studies

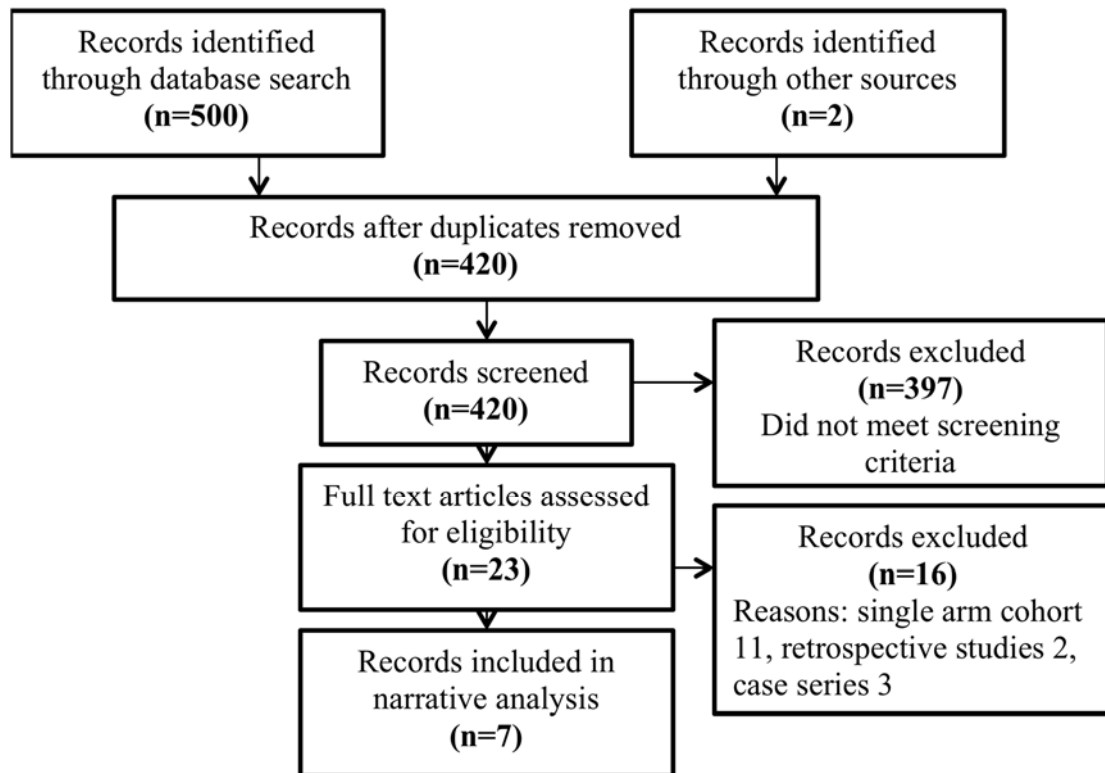
Two reviewers (GPO and EGB) determined the risk of bias in individual studies using the Cochrane risk of bias tool (see Appendix 1). (27) Six domains of the study design and reporting were assessed: random sequence generation for randomisation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and selective reporting (27). With this tool, studies are classified as high, unclear (where the domains were not clearly described) or low risk of bias (27).

3. Results

3.1 Studies included

We identified 420 unique studies through the searches, and examined full text of 23 studies. Seven RCTs, representing 427 participants met our inclusion criteria (Figure 1).

Figure 1: Flowchart of study selection based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.



3.2 Characteristics of the studies included

All studies were RCTs comparing a somatostatin analogue (six octreotide; one lanreotide) with either placebo (7, 28, 29) or hyoscine butylbromide (8, 16, 17, 24). Three RCTs compared a somatostatin analogue with placebo, two octreotide (7, 28) and one lanreotide. (29) Four RCTs compared octreotide with hyoscine butylbromide. (8, 16, 17, 24) A somatostatin analogue was administered to 220 participants, and placebo or hyoscine butylbromide to 207 (tables 2 and 3).

Five trials were multi-centre, (7, 16, 17, 28, 29) and two trials were single centre studies. (8, 24,) Five studies were conducted in Europe, (, 16, 17, 24, 28, 29) one in Australia (7) and one in China. (8)

Table 2: Overview of methods and findings of included Phase 3 studies which were designed to test efficacy and recruited to power

Study	Setting	Participants characteristics	Intervention	Comparator	Outcome Measure	Main results	Adverse effects	Risk of bias
Trials with documented adequate power (≥80%)								
Currow DC, et al. ⁷	12 palliative care service networks in Australia.	87 adults patients with vomiting secondary to inoperable MBO and where further anticancer treatments were not immediately appropriate.	Subcutaneous infusion of octreotide (600 mcg/24 hours); n=45	Placebo (subcutaneous infusion of normal saline); n=42	1. Primary outcome: number of days free of vomiting as reported daily by patients measured 72 hours after the first administration of study medications.	1. Primary outcome: No statistically significant difference in: - The number of days free of vomiting between groups (P=0.71); - Total number of people free of vomiting for all 72 hours (octreotide, n=17 and placebo, n=14; P=0.67) - Mean (SD) number of days free of vomiting in each group (1.87 [1.10], octreotide and 1.69 [1.15], placebo; P=0.47). 2. Secondary outcomes: - Both groups showed significant decrease in the mean unadjusted	No NCI CTCAE grade 3 or 4 toxicities	Low in all 6 domains
Blind, Placebo-Controlled, Randomized Trial of Octreotide in Malignant Bowel Obstruction. 2015	Recruited from Aug 2008 to May 2012		Both groups received standardized therapies: (regular parenteral dexamethasone [8 mg/24 hours], ranitidine [200mg/24 hours], and hydration [10-20 mL/kg/day unless overtly dehydrated at study entry).		- Patient rated Global Impression of Change; - The number of patient-reported episodes of vomiting; - Episodes of vomiting per day, - Survival; - Nausea; - Brief Pain Inventory - Functional status (Australia-modified Karnofsky Performance Status) scale; - Protocol defined as-needed symptom			

control medications.

number of vomiting episodes

between baseline and Day1;

- Adjusted multivariate regression

analysis: the octreotide group

experienced significant reduction in

the number of episodes of vomiting

compared with the placebo group

(IRR=0.40; 95% CI: 0.19-0.86;

P=0.019).

- Global Impression of Change:

Both groups reported a positive

daily change in outlook; 31 of 42

(74%, octreotide) and 31 of 37

(84%, placebo) rated their GIC > 0.

Both groups were likely to report a

positive daily change in outlook

(OR=1.8; 95% CI: 1.39-2.36; P <

0.001) but there was no difference

between the groups (P > 0.75).

- No difference in pain and nausea

(P=0.37) between the groups on any

day

- People in the octreotide group were 2.02 (P=0.004) times more likely to be administered hyoscine butylbromide each day compared to the placebo group. By study end, the OR between groups rose to 3.24 (95% CI: 1.06 - 9.96; P=0.041). The average number of doses/participant/group at study end was 0.51 (octreotide) and 0.17 (placebo).

- The median performance status in both groups was 50

- No difference in survival between groups at last census date (HR=1.24; 95% CI: 0.81 - 1.92; P=0.33).

Study	Setting	Participants characteristics	Intervention	Comparator	Outcome Measure	Main results	Adverse effects	Risk of bias
Mariani P, et al ²⁹ Symptomatic treatment with lanreotide microparticles in inoperable bowel obstruction resulting from peritoneal carcinomatosis: a randomized, double-blind, placebo-controlled phase III study. 2012	22 hospitals across Belgium, France, and the Netherlands. Recruitment was between 24/09/2003 and 15/09/2008.	80 adults, with peritoneal carcinomatosis who had an inoperable MBO and were experiencing two or more episodes of vomiting per day or had an NGT. They were withdrawn from the study if NGT was inserted during the 1st 7 days of the study.	Double-blind phase (10 days): Day 1: A single intramuscular lanreotide microparticles formulation 30mg injection.; n=43 (28 of whom had NGT at baseline) Open-label phase (n=59) Lanreotide every 10 days until they decided to stop treatment or died. Concomitant treatments were standardized at baseline to ensure comparability of treatment groups.	Placebo (as intramuscular injection); n=37 (23 of whom had NGT at baseline)	<i>1. Primary outcome:</i> - Proportion of patients with one or fewer vomiting episodes/day at day 7 or who had no recurrence of vomiting after NGT removal for 3 consecutive days during days 1 through 7 in both cases). (As assessed from diary card information) <i>2. Secondary outcomes:</i> - Changes from baseline in daily vomiting frequency (patients without NGT at baseline) or secretion volumes from NGT (patients with NGT at baseline); - Number of nausea episodes; - Abdominal pain intensity; - Well-being; - Number of days without vomiting; - Time to onset of symptom improvement; - Duration of symptom relief.	<i>1. Primary outcome:</i> More patients receiving lanreotide than placebo were achieved primary outcome (41.9% [n=43] vs 29.7% [n=37]) for the intent-to-treat (ITT) population on the basis of patient reports diary cards, but the difference between the groups was not statistically significant (odds ratio, 1.75; 95% CI, 0.68 to 4.49; P=0.24) <i>2. Secondary outcomes:</i> - Statistical significance for the corresponding supportive per protocol analysis (57.7% [n=26] vs 30.4% [n=23]; P<0.05) and ITT analysis, on the basis of investigators' assessments (50%	Dry mouth, Mild Diabetes Mellitus	Low in 4 domains, high in 1 domain and unclear in 1 domain

<p>(End points were assessed by visits scheduled at days 0, 3, 7, 10 (double-blind phase), and 20 (open label phase), Patients recorded symptoms on diary cards. A clinical examination was performed at all visits; information on adverse events (AEs) was collected at all visits except day 0.)</p>	<p>[n=43] vs 28.6% [n=37]; P<0.05);</p> <p>- Wellbeing: Using pre-specified analyses, differences between groups were significant for days 3 (difference in VAS 8.8 mm; 95% CI, 0.4 to 17.2 mm; P=04), 6 (difference in VAS 10.4 mm; 95% CI, 0.6 to 20.2 mm; P=0.004), and 7 (difference in VAS: 13.2 mm; 95% CI, 3.3 to 23.1 mm; P=0. 01), but the treatment difference between overall means was not significant (P=0.07).</p> <p>- No significant differences were observed for other secondary endpoints.</p>
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Table 3: Overview of methods and findings of included Phase 2 studies which were not designed to test efficacy (no power calculation) and/or did not recruit to power

Study	Setting	Participants characteristics	Intervention	Comparator	Outcome Measure	Main results	Adverse effects	Risk of bias
Trials with unstated or inadequate power								
Mercadante S, et al ¹⁷	Home care and surgical or oncological ward, in consultation with the palliative care team in Italy	18 patients with inoperable MBO received intervention or comparator drug. 15 analysed	Octreotide 300 mcg/24 hours subcutaneously; n=9	Hyoscine butylbromide 60 mg/24 hours; n=6	<p><i>1. Primary outcome:</i></p> <p>- Reduction in the number of episodes of vomiting at T0, T1 [24hours], T2 [48hours] & T3 [72hours].</p> <p><i>2. Secondary outcome:</i></p> <p>- Intensity of nausea, drowsiness, pain measured at the beginning of treatment and 24 hours, 48 hours, and 72 hours using a Likert scale 0 to 4:</p> <p>- Daily amounts of fluids administered intravenously or subcutaneously were also documented.</p>	<p><i>1. Primary outcome:</i></p> <p>Significant difference in episode of vomiting between the groups at T1 (Mean [SE] of episode of vomiting of 1.3[0.5] in the octreotide and 4.3[0.8] in the group Hyoscine butylbromide, P=0.01) and T2 (Mean [SE] of episode of vomiting of 0.4[0.2] in the octreotide group and 2.8[0.7] hyoscine butylbromide, P=0.004). No significant difference at reported at T3 (Mean [SE] of episode of vomiting of 1.0[0.6] in the</p>	None stated	Unclear in all 6 domains

octreotide group and 2.4[0.7] in the hyoscine butylbromide, $P>0.5$).

2. Secondary outcomes:

- Significant reduction in the intensity of nausea in octreotide group at T1, T2 and T3 ($P=0.01$) and significant difference between the groups at T2 and T3 ($P=0.02$ and 0.03 , respectively), No significant difference at T1

- No significant changes in dry mouth, drowsiness and colicky pain at T1, T2 and T3.

-Continuous pain was significantly lower in the octreotide group than the hyoscine butylbromide group at T1 ($p<0.05$), and at T2 ($P<0.01$). There was no significant difference at T3.

-Drowsiness was lower in the hyoscine butylbromide group compared to the octreotide group at

T2 ($p=0.04$). There was no
significant difference at T1 and T3

Study	Setting	Participants characteristics	Intervention	Comparator	Outcome Measure	Main results	Adverse effects	Risk of bias
Ripamonti C, et al. 16 Role of octreotide, scopolamine butylbromide, and hydration in symptom control of patients with inoperable bowel obstruction and nasogastric tubes: a prospective, randomized trial. 2000	Patients were recruited from Milan (Oncological Surgery Divisions of the National Cancer Institute) and Palermo (home care), Italy.	17 patients with NGT and inoperable MBO	Octreotide 300 mcg/ 24hrs for 3 days by a continuous subcutaneous infusion by means of a syringe driver; n=9 (4 in Milan, hospital care and 5 in Palermo, home care).	Hyoscine (Scopolamine) butylbromide, 60 mg/24 hours for 3 days by a continuous subcutaneous infusion by means of a syringe driver; n=8. (3 in Milan hospital care and 5 in Palermo home care)	1. Primary outcome: daily volume of GI secretions through a NGT, 2. Secondary outcomes: - The intensity of: continuous pain; colicky pain; nausea: dry mouth; thirst; dyspnoea; feeling of abdominal distension; and drowsiness at (T0) and then daily for 3 days (T1, T2, T3).	1. Primary outcomes: - NGT secretion: There was a significant secretion reduction in the patients treated with octreotide at T2 (P=0.016, 95% CI 319.5–950.5), and at T3 (P=0.020, 95% CI 298.2–861.7). (Efficacy between the groups was compared in only 10 patients) 2. Secondary outcomes: - No significant difference in continuous and colicky pain between the octreotide group and the hyoscine butylbromide group. - Nausea intensity in the 5 home care patients treated with octreotide at T2 was lower (P=0.05) compared to 5 home care patients on hyoscine butylbromide. - There was no relation between the intensity of nausea and the octreotide or hyoscine butylbromide, treatment in the hospitalized patients.	None stated	Unclear in 4 domains, low in 1 domain and high in 1 domain

- No significant changes were observed in dry mouth, thirst, drowsiness, intensity of dyspnoea and feeling of abdominal distension.

Study	Setting	Participants characteristics	Intervention	Comparator	Outcome Measure	Main results	Adverse effects	Risk of bias
Peng X et al ⁸ Randomized clinical trial comparing octreotide and scopolamine butylbromide in symptom control of patients with inoperable bowel obstruction due to advanced ovarian cancer.	Department of general surgery, Qilu Hospital of Shandong University, China between January 2010 and December 2013.	96 patients with recurrent ovarian cancer and inoperable MBO; life expectancy greater than 2 months.	Octreotide 300 mcg/24 hours by a continuous subcutaneous infusion; n=48. Concomitant treatment in both groups included NG tube and intravenous fluids.	Hyoscine (scopolamine) butylbromide 60 mg/24 hours by a continuous subcutaneous infusion; n=49.	1. Outcomes (NB: no stated primary outcome): - NGT secretions measured or the number of episodes of vomiting at (T0), 24 hours (T1), 48 hours (T2), and 72 hours (T3). - Intensity of nausea (T0), 24 hours (T1), 48 hours (T2), and 72 hours (T3); - Dry mouth; - Drowsiness; - Continuous pain and colicky pain.	1. Primary outcomes: - NGT secretions in the octreotide group were significantly less than that in the hyoscine butylbromide group at T1 (Mean[SD] volume in octreotide group of 563.6[315.1] and hyoscine butylbromide group of 1,206.9[278.2]; p<0.05), T2 (Mean[SD] volume in octreotide group of 355.4[205.4] and hyoscine butylbromide group of 808.5[312.6]; p<0.05), and T3 (Mean[SD] volume in octreotide group of 298.5[189.2] and hyoscine butylbromide group of 783.4 [258.6];P<0.05). - The number of episodes of vomiting in the octreotide group was significantly less	None stated	Unclear in 4 domains and low in 2 domains

than that in the hyoscine butylbromide group ($P<0.05$) at T1 (Mean[SD] volume in octreotide group of 1.5[0.3] and hyoscine butylbromide group of 4.1[0.7]; $P<0.05$) and T2 (Mean[SD] volume in octreotide group of 0.5 [0.3] and hyoscine butylbromide group of 2.3 [0.6]; $P<0.05$). No statistically significant difference at T3 (Mean[SD] volume in octreotide group of 1.2[0.5] and hyoscine butylbromide group of 2.0[0.8]; $P>0.05$).

2. Secondary outcomes:

- Significant reductions in the number of episodes of vomiting in the octreotide group from baseline at T1, T2, and T3 ($P<0.05$), whereas the reduction from baseline was significant only at T3 in the hyoscine butylbromide group ($P<0.05$).

- The intensity of nausea was significantly lower in the octreotide group than in the hyoscine butylbromide group at T2 and T3 ($P<0.05$).

-Continuous pain values were significantly lower in the octreotide group than in the scopolamine butylbromide group at T2 and T3 (P<0.05).
- No significant changes were observed in dry mouth, drowsiness, and colicky pain.

Laval G et al ²⁸	Multicentre study in 18 centres in France, between November 2005 and September 2008.	64 adults with inoperable symptomatic MBO due to peritoneal carcinomatosis of any origin; life expectancy greater than 1 month. (Planned to recruit 102 patients).	Octreotide 600 mcg/24 hours on days 1 to 6) Intramuscular octreotide LAR 30mg on days 1, 29, 57); n=32. Concomitant treatment in both groups: methylprednisolone 3-4mg/kg/24 hours intravenous bolus on days 1-6.	Placebo on days 1 to 6; n=32. (Matching Intramuscular placebo to immediate-release octreotide and octreotide LAR.	<i>1. Primary outcome:</i> - Proportion of patients at day 14 in each arm with treatment success: Absence of a nasogastric tube, and vomiting less than twice per day and no use of anticholinergic agents.	<i>1. Primary outcome:</i> - Treatment success at day 14 was achieved in 12/32 and 9/32 patients in the octreotide and placebo arms, respectively. No statistical analysis	Severe hyperglycaemia, (n=1) injection site erythema (n=1), mild local reaction (n=1)	High in 3 domains, low in 2 domains and unclear in one domain
Study	Setting	Participants characteristics	Intervention	Comparator	Outcome Measure	Main results	Adverse effects	Risk of bias

Mystakidou K et al ²⁴	Palliative unit in a hospital, Athens, Greece.	68 adults with advance cancer, not for further anti-tumour treatment, diagnosed with bowel obstruction.	Octreotide 600 - 800 mcg/24 hours; n=34. Concomitant treatment in both groups included Chlorpromazine 15-25 mg/24 hours subcutaneously.	Hyoscine butylbromide 60-80 mg/24 hours subcutaneously; n=34.	1. <i>Primary outcome:</i> Nausea scored as 1(mild), 2(average), 3(severe) and the number of vomiting episode/day. Measured at T1 (baseline), T2 (day 3), T3 (day 6) and T4 (1 day before death). 2. <i>Secondary outcomes:</i> pain intensity (using visual analogue scale 0-10); fatigue (reported as minor or major); and anorexia (minor or major). In addition electrolyte measurements on T1, T2 and T3.	1. <i>Primary outcomes:</i> - Mean percentage change from T1 to T2 of nausea scores and vomiting episodes were significantly different between the groups (nausea: octreotide group 93.4% and hyoscine butylbromide 84.2%; p=0.007 and episodes of vomiting octreotide group 82.8% and hyoscine butylbromide 67.0%; p=0.003). There was no significant difference between the groups at T3 (p=0.45) and T4 (p=0.84). 2. <i>Secondary outcomes:</i> - Pain: No significant difference between the groups at T1 to T2, T1 to T3 and T1 to T4. - Fatigue and anorexia: Octreotide group showed significantly higher improvement	Minor skin reaction (n=7)	Unclear in 5 domains and low in 1 domain
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than the hyoscine butylbromide

group at T1 to T2, T1 to T3 and

T1 to T4.

Abbreviations: NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Effects, MBO: Malignant Bowel Obstruction, ITT: Intention-to-treat, NGT: Nasogastric Tube, AE: Adverse Events, mcg: micrograms, mg: milligrams, VAS: Visual Analogue Scale.

3.3 Effectiveness of somatostatin analogues as compared to placebo and/or other pharmacological agents

Due to differences in the interventions and outcome measures across the included studies a meta-analysis was not possible. A narrative analysis was therefore performed (tables 2 and 3).

3.3.1 Effect of somatostatin analogues on vomiting

3.3.1.1 Placebo comparator studies

Placebo controlled trials are imperative when there is no gold-standard, evidence-based therapy. (69) This is the case for somatostatin analogues.

Two studies, one octreotide and one lanreotide, showed no significant difference between a somatostatin analogue and placebo for their primary endpoint. (7, 29) These studies included 87, (7) and 80 (29) participants. The octreotide vs placebo study found no statistically significant difference in the number of days free of vomiting (the primary endpoint) between the groups ($P=0.71$). It also found no statistical difference in the mean number of days free of vomiting in each group (mean [SD] number of days free of vomiting in each group (1.87 [1.10], octreotide and 1.69 [1.15], placebo; $P=0.47$); and total number of people completely free of vomiting for 72 hours (octreotide, $n=17$ and placebo, $n=14$; $P=0.67$). (7) A multivariate regression analysis however showed a significant reduction in the number of episodes of vomiting in the octreotide compared with placebo group. In the Global Impression of Change, both groups reported a positive daily change in outlook but there was no difference between the groups ($P>0.75$). (7)

In the lanreotide vs placebo study, (29) a single dose of intramuscular lanreotide microparticles was shown to be no better than placebo (41.9% [$n=43$] vs 29.7% [$n=37$]; $p=0.24$) with regard to the proportion of patients with one or fewer vomiting episode/day or no recurrence of vomiting after NGT removal for 3 consecutive days (the primary endpoint), using an intention to treat analysis (ITT) on day 7. There was however statistical significance for the corresponding *per protocol* analysis (57.7% [$n=26$] vs 30.4% [$n=23$]; $P<0.05$) and ITT analysis, on the basis of investigators' assessments (50% [$n=43$] vs 28.6% [37]; $P<0.05$). (29) Due to off-protocol change of concomitant of treatments standardized at baseline and missing data 39% of participants were excluded from the per protocol analysis. (29)

Although the phase II RCT that used a combination of immediate release octreotide and octreotide LAR or placebo met inclusion criteria, it did not complete recruitment. (28) Only 64 of the planned 102 participants were enrolled in the study, 28 of whom withdrew from the study by day 14. Furthermore, a comparative analysis was not carried out but it was reported that at day 14, 38% and 28% of patients were successfully treated with somatostatin analogues and placebo respectively. (28)

3.3.1.2 Active comparator studies

Four studies reported significant reduction in episodes of vomiting or NGT secretions in the octreotide group as compared to the hyoscine butylbromide group. (8, 16, 17, 24) Two of the studies measured the episodes of vomiting, (17, 24) one measured both episodes of vomiting and NGT secretions, (8) and one measured the volume of NGT secretions. (16) The number of participants in the four studies ranged from 17 to 96.

One of the studies reported a significant difference in mean percentage change

from baseline of episodes of vomiting (octreotide group 82.8% and hyoscine butylbromide group 67%; $p=0.007$) and nausea scores (octreotide group 93.4% and hyoscine butylbromide group 84.2%; $p=0.003$) between the groups from baseline to day 3, in favour of the octreotide group. This difference was however not sustained on day 6 ($p=0.45$) or on the day before death ($p=0.84$). (24) Another study that measured episodes of vomiting reported significantly greater reduction in the octreotide group as compared to hyoscine butylbromide group at 24 hours (mean [SE] of episode of vomiting of 1.3 [0.5] in the octreotide and 4.3 [0.8] in the group Hyoscine butylbromide; $P=0.01$) and 48 hours (mean [SE] of episode of vomiting of 0.4 [0.2] in the octreotide group and 2.8 [0.7] hyoscine butylbromide; $P=0.004$). There was however no difference between the groups at 72 hours (mean [SE] of episode of vomiting of 1.0 [0.6] in the octreotide group and 2.4 [0.7] in the hyoscine butylbromide, $P>0.5$). (17) For the study that measured NGT secretions data from only 10 home care patients were analysed. Octreotide, compared to hyoscine butylbromide, significantly reduced NGT secretions at 48 hours ($P=0.016$, 95% CI 319.5–950.5), and at 72 hours ($P=0.020$, 95% CI 298.2–861.7). (16) The study that measured both NGT secretion and episodes of vomiting reported that NGT secretions in the octreotide group were significantly less than in the hyoscine butylbromide group at 24 hours (mean [SD] volume in octreotide group of 563.6[315.1] and hyoscine butylbromide group of 1,206.9[278.2]; $p<0.05$), 48 hours (mean [SD] volume in octreotide group of 355.4[205.4] and hyoscine butylbromide group of 808.5[312.6]; $p<0.05$) and 72 hours (mean [SD] volume in octreotide group of 298.5[189.2] and hyoscine butylbromide group of 783.4 [258.6]; $P<0.05$) and the episodes of vomiting at 24 hours (mean [SD] volume in octreotide group of 1.5[0.3] and hyoscine butylbromide group of 4.1[0.7]; $P<0.05$) and 48 hours (mean [SD] volume in octreotide group of 0.5 [0.3] and hyoscine butylbromide group of 2.3 [0.6]; $P<0.05$) but no statistically significant difference at 72 hours (mean [SD] volume in octreotide group of 1.2[0.5] and hyoscine butylbromide group of 2.0[0.8]; $P>0.05$). (8)

3.3.2 *Effect of somatostatin analogues on abdominal pain intensity and abdominal distension*

With regard to secondary outcomes, six of the included studies measured abdominal pain intensity. Four studies reported no significant difference in pain, (7, 16, 24, 29) however in one of the studies, patients receiving octreotide had more hyoscine butylbromide indicating that there might be an association between octreotide administration and colicky abdominal pain. (7)

Two studies reported continuous pain to be significantly lower in the octreotide group ($P<0.05$) whereas there was no significant difference in colicky pain. (8, 17) One study measured abdominal distension and found no significant difference with octreotide. (16)

3.3.3 *Drug related adverse effects*

Four of the included RCTs reported on drug related adverse effects. (7, 24, 28, 29) One found no Common Terminology Criteria for Adverse Effects (CTCAE) grade 3 or 4 toxicities. (7) Adverse effects were reported as follows: dry mouth in 1 out of 80 participants (29), mild diabetes mellitus in 1 out of 80 participants (29), minor skin reaction in 7 out of 68 participants (24), severe hyperglycaemia in 1 out of 64 participants (28), injection site erythema in 1 out of 64 participants (28) and; mild local reaction in 1 out of 64 participants (28) (tables 2 and 3).

3.4 Risk of bias within studies

The Cochrane risk of bias for the trials is shown in table 4. One trial had low risk of bias in all of the 6 domains, (7) another study had low risk of bias in 4 domains (29) five studies had high and/or unclear risk of bias in most domains (8, 16, 17, 24, 28)

Table 4: Assessment of risk of bias

Study	Random sequence generation	Allocation concealment	Blinding of participant and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Currow D C, et al, 2015 Power calculations shown	Low risk “Randomization schedules were developed for each site using random number tables, generated centrally. Participants were randomized in blocks of four by site in a 1:1 ratio.”	Low risk “Site pharmacists who opened the treatment schedules to prepare the intervention were otherwise not involved in patient care. Syringes were identical in volume and color”	Low risk “Clinical staff, assessors, and participants were all blinded to treatment allocations.”	Low risk “Clinical staff, assessors, and participants were all blinded to treatment allocations.”	Low risk “6 patients (6%) were removed from analysis due to protocol violation”	Low risk “Data reported on pre-defined primary outcome”
Mariani, P. et al, 2012 Power calculations shown	Low risk “Patients were randomly assigned to treatment according to two computer generated randomization lists created and held confidentially by the sponsor”	Low risk “The sponsor placed the visually indistinguishable treatments in numbered containers and dispatched them in randomization blocks to study sites”	Low risk “double-blind, placebo-controlled investigation”	Low risk “double-blind, placebo-controlled investigation”	Unclear risk 16% did not complete the study	high risk Although data reported on pre-defined primary outcome showed no difference between lanreotide and placebo and; there was discrepancy between primary and supportive analysis the concluded that “significantly more patients receiving 30 mg of lanreotide microparticles than placebo responded to treatment in terms of reduced vomiting for two of the three analyses conducted”.
Mercadante, S. et al, 2000	Unclear risk “Patients were randomly divided into two groups to receive octreotide (group O) or HB (group	Unclear risk No information	Unclear risk No information	Unclear risk No information	Unclear risk No information	Unclear risk Primary outcome not clearly predefined

	HB) treatment.”					
Ripamonti et al	Unclear risk Randomization was not described	Unclear risk Allocation concealment was not described	Unclear risk Not described	Unclear risk Not described	Low risk Although sample was small there was not loss to follow up	High risk Analysis of primary outcome was done on very small number of patients, only 10 of the 17 participants who followed up at home were analysed.
Peng, X. et al, 2015	Low risk “Randomization was achieved by means of computer generated random numbers”	Unclear risk No information	Unclear risk No information	Unclear risk No information	Low risk Only 1 of 97 patient withdrew	Unclear risk Primary outcome not clearly predefined
Laval, G. et al, 2012	High risk “Despite the process of randomization, a higher proportion of patients in the octreotide arm (46.4%) than in the placebo arm (21.9%) had a Karnofsky score less than 50”	Unclear risk No information give	High risk “Because octreotide LAR has a different appearance to the placebo, the nurse who administered the treatments was not blinded”	Low risk “Neither the investigator nor the patient was informed of the patient’s assigned group. The assessment of symptoms was performed by the patient and investigator”	High risk 28 out of 64 (~44%) patients did complete the study.	Low risk “The primary endpoint was determined in the intention-to-treat (ITT) population at day 14.
Mystakidou, et al, 2002.	Unclear risk Randomization sequence generation method not described	Low risk “The clinician were unaware of which group the patients were assigned to”	Unclear risk No information	Unclear risk No information	Unclear risk No information	Unclear risk 15 patients withdrew.

4. Discussion

This systematic review evaluated the evidence for the effectiveness of somatostatin analogues as compared to placebo and/or other pharmacological agents. We identified seven eligible RCTs of somatostatin analogues vs placebo or hyoscine butylbromide for the relief of symptoms due to inoperable MBO. (7, 8, 16, 17, 24, 28, 29)

The design, outcome measurement and timing of endpoints varied between studies. Therefore, as a meta-analysis was not possible, each trial’s individual contribution to the evidence base was evaluated. Five trials with high Cochrane risk of bias provided lower level evidence of benefit (8, 16, 17 24, 28) and two trials with low Cochrane risk of bias provided higher level evidence of no benefit. (7, 29)

4.1 Outcome measurement and study endpoints

The primary outcome measurement varied from NGT secretion volume, to number of vomits per day and was measured at varying follow up time points. The choice of primary outcomes appeared to be empirical: as pointed out by Currow and colleagues, there is no agreed clinically relevant outcome measure or time-point for nausea and vomiting in the palliative care setting. (7, 62) Debate continues as to when a benefit would be expected, for how long any benefit would be sustained, and what benefit would be considered clinically relevant by the patients concerned and their family members. (59) Further, the natural history of MBO is still largely unknown; (34) although the placebo arms of the reported trials give important information for the length of follow up reported. In the studies reporting benefit, this tended to be early during follow up and was not sustained much beyond day 3. (8, 16, 17, 24) Even if this benefit was to be confirmed in subsequent studies, there is an important clinical question regarding whether people with vomiting due to MBO should or can be supported over the weeks leading up to their death by medical management alone. It is not known whether medical management confers net benefit, including patient acceptability, over gut decompression by whatever means: the trials have not been conducted.

Two studies reported no difference between somatostatin analogues and placebo in their primary endpoints. (7, 29) One study's primary outcome was the number of days free of vomiting measured at 72 hours whereas episodes of vomiting was a secondary outcome. (7) The reported results showed efficacy of octreotide in reducing episodes of vomiting but not number of days free of vomiting. The correct timing of this outcome measurement has been debated. (58) Whereas some authorities recommend that 2 to 5 days are required for octreotide to show effect, (57) from this review, earlier benefit, if present, was not sustained in those studies that measured outcome after 3 days. It has been suggested that this could be partly due to worsening symptoms due to disease progression. (59) The study that measured endpoint at baseline, day 3, day 6 and 1 day before death, found no difference between octreotide and hyoscine butylbromide at day 6 and 1 day before death. (24) Four studies measured outcome only up to 3 days, (7, 8 16, 17) one of which showed no difference between octreotide and hyoscine butylbromide at day 3 also suggested that the difference tended to be less pronounced after 3 days. (16)

Hyoscine butylbromide was used as an as-needed therapy for colicky pain at a dose per participant of 0.51 for the octreotide group and 0.17 with placebo group but it is also an anti-secretory drug. (7) This could have therefore biased outcome in favour of the octreotide group.

4.2 Study design

4.2.1 Robustness

There are a number of cohort studies, retrospective reviews, and single-patient reports that did not meet the standard required for this review. These suggest improvement in symptoms due to MBO with somatostatin analogues. (16-18, 31-50) These studies with high risk of bias do not provide robust evidence of effectiveness of somatostatin analogues; they are uncontrolled, have high risk of bias and do not have a comparator. (51) Where there is an urgent clinical need to attempt to alleviate distressing symptoms, there is a temptation to base practice on preliminary data. Some authors have advocated for balanced and practical considerations in the design,

conduct and interpretation of clinical research in palliative care. (59, 60, 61, 62) However, as Keeley urges, [64] we must be wary of the “faggot fallacy”. [65] For those unfamiliar with this English term, a faggot is a bundle of sticks tied together; a collection of pieces of weak evidence does not make them stronger for being grouped together. Kunz et al reported that failure to adequately conceal random allocation could make the apparent effects of care seem either larger or smaller than they really are. (69) Further, the International Conference on MBO and Clinical Protocol Committee advocates that high quality studies that ultimately improve symptom management strategies are required. (5) The Consolidated Standards of Reporting Trials (CONSORT) guidelines were written to help the reporting and interpretation of RCTS in order to minimize the risk of biased estimates of treatment effects. [66] Thus, in this review we have followed the Cochrane risk of bias tool, based on the CONSORT guidance to act as a compass through this difficult topic where there is an urgent need for therapeutic options at the bedside. We have reported our findings transparently using standard guidance. Of the seven trials, only two were a phase III multisite trials with adequate power to discard the null hypothesis *and* reached their required sample size. (7, 29) These were the only two with a low risk of bias in all or most domains assessed. It is also important to note the multisite nature of these trials. Single centre trials, especially smaller ones, show larger intervention effects than multicentre trials (67); the two small trials in this review (N=10 and N=18 of which only 10 were analysed (16, 17)) both showed benefit with octreotide. Multicentre trials tend to have a more heterogeneous population and therefore provide more generalizable findings, which can be more readily implemented in clinical practice. (71) The five studies categorized as high or unclear risk of bias had absent or inadequate reporting of allocation concealment, blinding, MBO diagnosis and evaluation of participants who were excluded due to lack of efficacy. We recognize that inadequate reporting of a trial may not equate to poor trial design, however, as Altman and colleagues stated, “Critical appraisal of the quality of clinical trials is possible only if the design, conduct, and analysis of RCTs are thoroughly and accurately described in published articles.” (73) It is therefore inevitable that more weight is given to the findings of the two adequately powered trials with regard to their primary outcome as the robust design allows more confidence in the findings. However, the question in both of these trials remains as to whether their respective primary endpoints are the most clinically relevant, and whether the empirical nature of both sample size calculations was adequate.

4.2.2 Analysis

The study by Mariani *et al* had discrepancies in the analysis of its primary outcome. The intention to treat (ITT) analysis showed no difference between the two groups, whereas the *per protocol* analysis and investigator’s subjective assessment of responders at day 7 showed efficacy in reducing vomiting. (29) In the *per protocol* analysis, the number of included participants was 39% less than the ITT population. (ITT: Lanreotide 43, placebo 37; *per protocol*: Lanreotide 26, placebo 23). (29) One of the most common reasons for exclusion from the *per protocol* population was an off-protocol change of concomitant of treatments standardized at baseline to ensure group comparability, i.e. (i) intravenous corticosteroids (ii) intravenous proton pump inhibitors (iii) antispasmodics or antiemetics. (29) This is likely to lead to the improved outcomes reported in the *per protocol* population. Furthermore any *per protocol* analysis is more likely to show benefit than the same study analysed on an intention to treat basis. (72)

4.3 Adverse events

In general, somatostatin analogues appeared to be tolerated with a few mild adverse events and no drop outs due to toxicity reported in any of RCTs to be anything other than. However, it is of note that the observed increased use of hyoscine in the octreotide arm of the Currow *et al* study, in addition to risking overestimate of benefit in that arm, might have been due to increased colicky abdominal pain. (7)

5. Limitations

The main limitation of this systematic review is that a meta-analysis could not be performed due to differences in interventions and outcomes. Some included studies had a high risk of bias, but due to the paucity of RCT data in this area, we did not exclude trials on the basis of quality of reporting. (27)

It is possible that some relevant studies were missed despite a detailed search strategy where there were no date or language restrictions and standard methods for selection and data extraction were employed.

6. Implications for further research

There is a need for work to understand what people with nausea and vomiting due to MBO class as a clinically important outcome. Questions should be asked in the context of what makes a meaningful difference to overall function, wellbeing and possibilities for place of care. For example, the number and volume of vomits may need to be greatly reduced in order for that person to remain at home, especially if they live alone. As we do not have high level evidence of efficacy against placebo, trial equipoise remains and further placebo controlled trials are needed. This will also help our understanding of the natural history of MBO; misattribution of benefit to intervention (a recognized concern in palliative care trials, 74) will lead to overestimation. We also need to clarify the role of and acceptability of gut decompression as a more definitive measure, given that death may not ensue for several weeks. This better understanding would inform study design in order to inform clinical practice and service provision. Agreement on common outcome measures would help collaborative working between centres, or at least allow the possibility of data pooling and meta-analysis to allow our knowledge to move forward. Further research should be mindful that the onus is on the researchers to demonstrate net benefit

7. Conclusions

Using standardized tools for risk of bias, we found low level evidence of benefit with somatostatin analogues in the symptomatic treatment of MBO. However, high level evidence from trials with low risk of bias found no benefit for their primary outcome. There is debate regarding the clinically relevant study endpoint for symptom control in MBO. The International Conference on MBO and Clinical Protocol Committee calls for adequately powered, well designed trials with agreed clinically important endpoints and measures which can underpin recommendations for practice. The role of somatostatins (whether, and, if so, what) in this challenging and distressing clinical situation requires clarification.

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Appendix 1: Cochrane risk of bias tool

Domain	Support for judgement	Review authors' judgement
<i>Selection bias.</i>		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
<i>Performance bias.</i>		
Blinding of participants and personnel <i>Assessments should be made for each main outcome (or class of outcomes).</i>	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
<i>Detection bias.</i>		
Blinding of outcome assessment <i>Assessments should be made for each main outcome (or class of outcomes).</i>	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
<i>Attrition bias.</i>		
Incomplete outcome data <i>Assessments should be made for each main outcome (or class of outcomes).</i>	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
<i>Reporting bias.</i>		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.

<i>Other bias.</i>		
Other sources of bias.	<p>State any important concerns about bias not addressed in the other domains in the tool.</p> <p>If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.</p>	Bias due to problems not covered elsewhere in the table.

Source: The Cochrane handbook for systematic reviews of interventions version 5.0.0 [updated February 2008], Chapter 8, Available from: <http://www.cochrane-handbook.org/>. Accessed 26 May 2015.