POSSIBLE DELETION – Section 1: Anaesthetics --

1.3 Preoperative medication and sedation for short-term procedures

PROPOSAL FOR DELETION OF PROMETHAZINE AS A PREMEDICATION AND/OR SEDATIVE FOR SHORT TERM ANESTHETIC PROCEDURES FROM WHO MODEL LIST OF ESSENTIAL MEDICINES

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Summary statement of the proposal
Proposal for deletion of promethazine as a premedication and/or sedative for short term anesthetic procedures from World Health Organization (WHO) Model List of Essential Medicines for adults (WHO, 2010).

Name of the organization preparing the application
School of Medicine, University of Split, Soltanska 2, 21000 Split, Croatia.

Medicine reviewed in proposal; International Nonproprietary Name of the medicine
The proposal provides an updated review of the evidence for and against the use of promethazine in adults and children as a premedication and/or sedative for short term anaesthetic procedures compared to placebo and/or other medicines used for these indications.

Additionally, this proposal will also provide an updated review of the evidence for and against the use of promethazine for the management of postoperative nausea and vomiting in adults and children compared to placebo and/or other medicines used for these indications.

Promethazine is a phenothiazine derivative available as a medicine since its introduction in 1946. It acts as a histamine H1-receptor antagonist with moderate muscarinic and dopamine (D2) receptor blocking activities. [1]

Promethazine is currently listed on the WHO Model List of Essential Medicines as a medicine used for preoperative medication and sedation for short-term procedures (WHO, 2010). Promethazine is not listed on the WHO Model List of Essential Medicines for Children (WHO, 2010).

In the WHO Model Formulary 2008, promethazine is listed as a medicine used for preoperative medication and sedation for short-term procedures. Other medicines listed for the same indication are atropine, diazepam, and morphine. It is also listed for the management of post-operative and drug induced vomiting. Promethazine was deleted from section 17.2 of the WHO Model List of Essential Medicines in 2009 on the ground of its lack of efficacy in postoperative nausea and vomiting. Promethazine is not listed in the WHO Model List of Essential Medicines for Children 2009 or the WHO Model Formulary for Children 2010.

International availability; Common brand names
Promethazine is available worldwide, in some countries as over the counter medicine, and in some only by prescription. The common brand names associated with promethazine are: Alergosan, Avomine, Atosil, Boipulmonale Simple, Crema Anitallergica Antipruriginosa, Diven, Doriless, Fargan, Fenergan, Fenergan Topico, Lisador, PCL, Phenadoz, Phenergan, Phenergan Expectorant, Promedyl, Prometazol, Promethegan, Rectoquintyl-Promethazine, Romergan, Tussisedal (Source: MARTINDALE® drug evaluations (www.micromedex.com))

Available formulations of the medicine
Injection: 25 mg (hydrochloride)/ml in 2-ml ampoule.
Oral liquid: 5 mg (hydrochloride)/5 ml.
Tablet: 10 mg; 25 mg (hydrochloride).
Indications for use

**Adult:** Treatment of allergies, adjunct to anesthesia, motion sickness, nausea and vomiting from any cause, adjunct to management of post-operative pain, general sedation, obstetric sedation.

**Child:** Treatment of allergies, treatment and prophylaxis for motion sickness, nausea and vomiting of known cause, adjunct to management of post-operative pain, general sedation.

(Source: DRUGDEX® evaluations (www.micromedex.com))

Contraindications and Precautions [2]

It is contraindicated to use promethazine in patients with known hypersensitivity to promethazine (cross reactivity with other phenothiazines may occur), in patients with severe toxic CNS depression or coma, and in children < 2 years.

Promethazine should be used with extreme caution in children, due to the potentially severe risk of respiratory depression. Sudden deaths in children have been associated with excessively high doses of promethazine. Therefore, the lowest effective doses are recommended to be used in children and concomitant use of other medications having respiratory depressant effects should be avoided.

Promethazine should not be given subcutaneously or intra-arterially due to severe local reactions including necrosis. Intravenous (I.V.) administration may also cause serious tissue reactions and it should be used only in emergency situations or when intramuscular or oral administration is contraindicated. Those veins should be large and patent. Rapid I.V. administration may produce a transient fall in blood pressure, and slow I.V. administration may produce a slightly elevated blood pressure. The preferred route of administration of injection is deep intramuscular injection.

Neuroleptic malignant syndrome (NMS) has been reported with promethazine when used alone or in combination with antipsychotic drugs.

Children with dehydration are at increased risk for development of dystonic reactions.

Use with caution in patients with cardiovascular disease, narrow-angle glaucoma, prostatic hypertrophy, bone marrow depression, impaired liver function, asthma, peptic ulcer, sleep apnea, and hypertensive crisis; avoid in patients with suspected Reye’s syndrome.

Promethazine may lower the seizure threshold so it should be used with caution in patients with seizure disorders or if they are receiving other medications which may also lower the seizure threshold.

Adverse Effects [2]

**Cardiovascular:** tachycardia, bradycardia, hypotension, hypertension, palpitations, angioneurotic edema; **CNS:** sedation, drowsiness, confusion, fatigue, excitement, extrapyramidal reactions, dystonia, tardive dyskinesia, NMS, hallucinations, insomnia, seizures, catatonic-like states, hysteria; **Dermatologic:** photosensitivity, rash, angioedema, urticaria; **Endocrine:** weight gain; **Gastrointestinal:** xerostomia, GI upset, increased appetite, abdominal pain, diarrhea, nausea; **Genitourinary:** urinary retention; **Hematologic:** thrombocytopenia, leucopenia, agranulocytosis; **Hepatic:** cholestatic jaundice, hepatitis; **Local:** thrombophlebitis; **Neuromuscular and skeletal:** arthralgia, tremor, paresthesia, myalgia; **Ocular:** blurred vision, diplopia; **Otic:** tinnitus; **Respiratory:** thickening of bronchial secretions, pharyngitis, respiratory depression, and apnea; **Miscellaneous:** allergic reaction.

Dosage regimens [3]

**Antiemetic medicine**

- For treatment of nausea and vomiting:
  - by mouth, ADULT, 25 mg at night, increased to 50–75 mg at night or 25 mg 2–3 times daily if necessary (maximum, 100 mg in 24 hours),
  - by deep intramuscular injection or by slow intravenous injection (diluted to 2.5 mg/ml in water for injection), ADULT, 12.5–25 mg, repeated at intervals of not less than 4 hours (usual maximum, 100 mg in 24 hours).

- For prevention of motion sickness:
- by mouth, **ADULT**, 20–25 mg at bedtime on night before travel, repeated on the morning of travel if necessary; **CHILD 2–5 years**, 5 mg at bedtime on night before travel and also on morning of travel if necessary; **CHILD 5–10 years**, 10 mg at bedtime on night before travel and also on morning of travel if necessary.

**Preoperative medication and sedation for short-term procedures**
- by mouth 1 hour before surgery, **CHILD over 1 year**, 0.5–1 mg/kg.

**Summary of available efficacy data**

**Identification of clinical evidence**

Medline, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials (1970 – June 2010), and the World Health Organization web page were searched to identify all published papers and reports evaluating the effectiveness of promethazine as a preoperative medication and sedative for short-term procedures, and its effectiveness for the management of postoperative nausea and vomiting in adults and children (Figures 1-4). Search terms were: promethazine, sedation, postoperative nausea and vomiting. The studies in languages other than English were excluded. Titles and then abstracts of retrieved papers were reviewed. Studies were included for review if they were systematic reviews or randomized controlled trials (RCTs). Clinical trials which are not RCTs were also included if the data published in them was considered relevant for this review. The citation lists of included studies were searched to identify any additional studies. The studies in which promethazine was used as a part of combination of medicines (for example, lytic cocktails) were excluded from review. Different medicines, doses, and regimens have been used in these studies and the findings cannot be used to make conclusion which agent is most effective for preventing postoperative nausea and vomiting or producing sedation. From the literature obtained, data relevant for evaluation of promethazine effectiveness was extracted and tabulated.
Figure 1. Flow diagram for identification of clinical trials evaluating the effectiveness of promethazine for the management of postoperative nausea and vomiting.
Figure 2. Flow diagram for identification of systematic reviews or meta-analysis evaluating the effectiveness of promethazine for the management of postoperative nausea and vomiting.
Figure 3. Flow diagram for identification of clinical trials evaluating the effectiveness of promethazine as a preoperative medication and sedative for short-term procedures.

Records identified through Medline (n = 8)

Additional records identified through Cochrane Central Register of Controlled Trials (n = 75)

Records after duplicates removed (n = 79)

Records excluded (n = 57)
The review of the titles and abstracts of these clinical trials did not indicate that they are evaluating the effectiveness of promethazine as a preoperative medication and sedative for short-term procedures or promethazine was used as a part of combination of medicines (for example, lycic cocktails or mepiridine + promethazine + chlorpromazine combination).

Records screened (n = 70)
Five non-English articles and four abstracts were excluded.

Full-text articles assessed for eligibility (n = 13)

Full-text articles excluded (n = 5)
Promethazine was used as a part of combination of medicines or for different indication than the one evaluated here.

Studies included in tabular presentation of clinical trials (n = 17)

Additional articles included by reference checking (n = 10)
The citation lists of previously included clinical trials and analysis of retrieved systematic reviews identified additional clinical trials evaluating the effectiveness of promethazine as a preoperative medication and sedative for short-term procedures.
Summary of comparative effectiveness in different clinical settings

Postoperative nausea and vomiting (PONV)

Postoperative nausea and vomiting (PONV), together with pain, is among the most important concerns of patients undergoing surgery. Nausea, vomiting, and retching can occur with all types of anesthesia (general, regional, or local). [4] The incidence is ranging from 30% to 50%, with numbers reported as high as 70% in higher-risk patients. [5] Consequences of PONV are numerous, and it can cause rupture of stitches, bleeding, electrolyte imbalances, dehydration, and aspiration of gastric contents. [6, 7] Patients who experience PONV also require additional health care. All of this could be a reason for delayed discharge from post-anesthesia care unit (PACU) or a reason for additional medical interventions, resulting in increased health care costs. Current strategies for prevention of PONV include: (a) proactive risk assessment, (b) avoiding PONV “triggers”, and (c) administration of prophylactic antiemetic medications. [4]
Apfel et al. created a risk assessment scoring system and included four patient-related risk factors in it: female gender, nonsmoking status, history of PONV or motion sickness, and postoperative use of opioids. Koivuranta et al. created similar scoring system, but with five factors: female gender, history of PONV, duration of surgery greater than 60 min, nonsmoking status, and history of motion sickness. The incidence of PONV correlates with number of risk factors a patient possesses. A pediatric scoring system has been designed by Eberhart et al. Risk factors associated with increased frequency of PONV in children are: duration of surgery ≥ 30 minutes, age ≥ 3 years, strabismus surgery, and a history of PONV in the patient, parent or sibling. Consensus panel guidelines, developed under the auspices of the Society of Ambulatory Anesthesia, recommended the prophylactic use of antiemetic therapy only for patients who are at moderate to high risk for developing PONV. None of the available antiemetics is entirely effective. If it is necessary to use combination therapy with more prophylactic drugs, then the drugs with different sites of activity should be used to optimize efficacy. All prophylaxis in children at moderate or high risk for postoperative vomiting should include combination therapy using a 5-HT3 antagonist and a second drug.

A modified and simplified treatment algorithm for the management of PONV is shown in Figure 5. Treatment of PONV includes various classes of medications, such as phenothiazines, antihistamines, butyrophenones, anticholinergics, benzamides, dexamethasone, and serotonin (5-HT3) antagonists. Newly available classes are opioid antagonists (naloxone, nelmeffene, alvimopan) and neurokinin-1 (NK1) receptor antagonists. However, confirmatory studies for these medicines are warranted. Prochlorperazine, promethazine, and perphenazine are commonly used phenothiazines. Promethazine offers the advantage of low cost, slow-intramuscular absorption, and long elimination half-life, making it potentially attractive for use in outpatient surgery.
Table 1. Clinical trials evaluating the effectiveness of promethazine for the management of postoperative nausea and vomiting

<table>
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<tr>
<th>RISK FACTORS</th>
<th>ADULT: female gender, nonsmoking status, history of PONV or motion sickness, postoperative use of opioids, and emetogenic surgery</th>
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<td>CHILDREN: duration of surgery ≥ 30 minutes, age ≥ 3 years, strabismus surgery, and a history of PONV in the patient, parent or sibling</td>
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- Consider
- Patient preferences
  - Cost effectiveness
  - Reducing baseline risks
  - Level of risk
- Patient risk
  - LOW: Wait and see
  - MEDIUM: Pick 1 - 2 interventions for adults or ≥ 2 for children
  - HIGH: ≥ 2 interventions; multimodal approach
- Possible options for prophylaxis and treatment
  - Propofol Anesthesia; Regional Anesthesia
  - Droperidol or Haloperidol
  - Promethazine, Prochlorperazine, Perphenazine
  - Propofol in PACU (rescue only)
  - Dimenhydrinate, Ephedrine, Scopolamine
  - Non-pharmacological: Acupuncture
  - 5-HT3 antagonist; Dexamethasone

TREATMENT OPTIONS:
- If prophylaxis fails or was not received: use antiemetic from different class than prophylactic agent
- Readminister only if > 6 hours after PACU; do not readminister dexamethasone or scopolamine

Figure 5. Treatment algorithm modified from Gan et al. [11]

After literature search and analysis of retrieved papers, 19 relevant clinical trials and 4 systematic reviews were identified evaluating the effectiveness of promethazine for the management of postoperative nausea and vomiting (Table 1., Table 2.).
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<th>No.</th>
<th>Article; Study Type; Study Design</th>
<th>Findings; Conclusion</th>
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<tr>
<td>01.</td>
<td><strong>Conner (1977)</strong> [14] Double-blind RCT Adults aged 18 – 70 years (N = 270) One hour before surgery, patients received morphine 5 mg or 10 mg alone or in combination with promethazine 6.25, 12.5, or 25 mg. Promethazine 25 mg alone also was studied.</td>
<td>The addition of promethazine to morphine had no effect on incidence of nausea which occurred in 5-10% of the patients in all groups, including patients who received promethazine alone. It was reported that there was no statistically significant difference between the various doses of promethazine, but the actual numbers were not stated.</td>
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<td>02.</td>
<td><strong>Dodson (1978)</strong> [15] Double-blind RCT Women aged 16 – 70 years (N = 124) As a premedication, 2-3 hours before surgery: 1. lorazepam 2.5 mg p.o. 2. promethazine 50 mg p.o.</td>
<td>Vomiting during anesthesia, or during the 1st hour after surgery occurred in 8 patients, of whom 7 received lorazepam (0.02&lt;P &lt; 0.05). There was no difference between the groups in respect of late PONV (p-value not stated).</td>
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<td>03.</td>
<td><strong>Vella (1985)</strong> [16] Double-blind RCT Women in labour (N = 477). Patients received pethidine (100-150 mg) i.m. along with either: 1. isotonic saline (2 ml, Control group) 2. promethazine 25 mg 3. metoclopramide 10 mg</td>
<td>Significantly more patients in the control group had nausea than in other groups in the 1st and 4th hours (p &lt; 0,001). The proportion vomiting in the placebo group was significantly different from that in the promethazine group in the 1st and 4th hours (p &lt; 0,001), and from that in the metoclopramide group in the 1st (p &lt; 0,001), 2nd, 3rd, and 4th hours (p &lt; 0,01). Both metoclopramide and promethazine prevented the increase in nausea and vomiting associated with pethidine administration, with promethazine having a more sustained effect - by 4 hours promethazine produced a significant reduction in nausea from the level before pethidine administration (p &lt; 0.05).</td>
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<td>04.</td>
<td><strong>Blanc (1991)</strong> [13] Double-blind RCT Children aged 2 – 10 years (N = 100; 47 M + 53 F) 1. droperidol 0.075 mg/kg i.v. + placebo i.m. 2. promethazine 0.5 mg/kg i.v. + promethazine 0.5 mg/kg i.m. (max. 25 mg)</td>
<td>The incidence of vomiting predischarge was 8% in group 1. and 2% in group 2, and it was reported as not significant (p-value not stated). The incidence of vomiting postdischarge and overall was significantly higher with droperidol (54% and 56%) than with promethazine (10%, 10%) (p &lt; 0,0001). Promethazine pretreatment reduces the incidence of postoperative vomiting in unpremedicated children undergoing outpatient strabismus correction.</td>
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<td>05.</td>
<td><strong>Silverman (1992)</strong> [17] RCT Women aged 18 – 60 years (N = 30) In patient care unit, patients were assigned to receive patient-controlled analgesia: 1. morphine 2. morphine+promethazine 0.625 mg with each morphine dose (an average of 17.6 mg over a 24-h period)</td>
<td>Visual analogue scale (VAS) scores for nausea were not significantly different between the two groups (p-value not stated). Mean VAS range in group 1. was from 1.4 to 0.6, and in group 2. from 2.1 to 1.0. The addition of promethazine to morphine was associated with a significant decrease in the symptom-therapy score for nausea. Group 1. patients had mean ± SD symptom-therapy scores of 2.4 ± 1.7; group 2. had 0.9 ± 1.5 (P &lt; 0,05).</td>
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<td>06.</td>
<td><strong>Sandhya (1994)</strong> [18] RCT Women aged between 22.4 ± 2.5 and 25.0 ± 4.88 years (N = 32) Patients received pentazocine 0.6 mg/kg i.v. 5 minutes</td>
<td>Vomiting was scored at the end of anesthesia (t1), one hour later (t2) and at the time of discharge (t3). The scores were comparable, not significantly different (p-value not stated). In group 1. vomiting score was at t1 4.00; at t2 3.82; and at t3 3.36. In group 2. the scores were 4.00; 4.00; 4.00;</td>
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For premedication the patients received:  
1. oral diazepam 5-15 mg + placebo patch  
2. oral promethazine 10 mg + placebo patch  
3. oral promethazine 10 mg + transdermal scopolamine patch 1.5 mg  
| In group 3. compared to group 2., the significantly lower were the incidence of nausea (P < 0.05), and the number of nausea episodes (P < 0.01). The incidence of vomiting and the number of vomiting episodes were significantly lower in group 3. compared both to groups 1. and 2. (P < 0.05). There were no differences between the groups in the severity of nausea or vomiting (p-value not stated).  
The combination of oral promethazine and transdermal scopolamine was most effective in reducing PONV symptoms and also reduced the need for postoperative pain treatment. |
Premedication before surgery:  
1. no treatment = Control group  
2. atropine 0,01 mg/kg i.m. + diazepam 0.2 mg/kg p.o.  
3. atropine 0,01 mg/kg i.m. + promethazine 1 mg/kg i.m.  
| 1 hour after surgery, the incidence of nausea and vomiting was significantly (P < 0.005) lower in group 3. (1 of 23; 0 of 23, respectively) compared to groups 1. (7 of 20; 5 of 20) and 2. (6 of 19; 6 of 19).  
There was no difference between groups 1. and 2.  P-value not stated).  
24 hours after surgery, significant difference (p < 0.05) was found for vomiting between group 3. (2 of 23) and groups 1. (9 of 20) and 2 (9 of 19). The difference was not significant for nausea (p > 0.05).  
The combination of promethazine and atropine was very effective in reducing occurrence of PONV. Promethazine is suggested as an effective and inexpensive medication to prevent PONV in orthopedic surgery. |
At induction of anesthesia, patients received:  
1. ondansetron 4 mg  
2. promethazine 25 mg  
3. promethazine 12.5 mg + ondansetron 2 mg  
4. placebo  
| First 1-2 hours after surgery, there were no differences between the groups having nausea, vomiting, or both p-value not stated).  
Over the 24-h period, the incidence of nausea was significantly reduced in promethazine (13%) and combination (17%) group compared with placebo group (42%; p < 0.05).  
Incidence of vomiting was significantly reduced in combination group (17%) compared with promethazine (35%), ondansetron (38%) and placebo group (63%) (p = 0.02).  
Incidence of combined nausea and vomiting was significantly different between the four groups (p = 0.03), and it was reduced in promethazine (39%; p = 0.03) and combination (29%; p = 0.003) group compared with placebo group (74%). There was no difference between placebo and ondansetron.  
The mean number of vomiting episodes (severity) was significantly reduced in the combination group (0.25 ± 0.68) compared with placebo (1.95 ± 2.61) (p-value not stated).  
Combination of ondansetron and promethazine and promethazine alone are effective and inexpensive choices. However, therapy with antiemetic medicines |
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Women aged 35 ± 9 years (N = 95)  
Patients received droperidol 0.5 mg i.v. intraoperatively, and prior to transfer from post-anesthetic recovery room:  
1. promethazine 0.6 mg/kg i.m.  
2. placebo | The incidence of nausea, vomiting, and rescue antiemetic use in the recovery room was similar between the groups (P > 0.05).  
There was no significant difference between the placebo and promethazine group in the incidence of experienced nausea at some time after discharge (51% vs 46%, respectively), worst level of nausea reported, moderate to severe nausea (32 vs 42%), vomiting (15 vs 19%), or the need for rescue antiemetics following discharge (28 vs 29%) (p-values not stated).  
Promethazine had no effect on postdischarge nausea scores, vomiting, or rescue antiemetic requirements. |
Adults aged between 46.7 ± 15.7 and 50.0 ± 15.3 years (N = 150; 59 M+91 F)  
Before emergence from general anesthesia, patients received PONV prophylaxis: droperidol 0.625 mg i.v. or placebo.  
If PONV occurred in the postanesthesia care unit, patients received rescue antiemetic (N = 31):  
1. droperidol 0.625 i.v.  
2. ondansetron 4 mg i.v.  
3. promethazine 12.5 mg i.v. | Significantly more people in placebo group (31 of 76; 40.8%) experienced PONV than in droperidol prophylaxis group (5 of 74; 6.8%) (p < 0.001).  
Analysis of 31 patients in placebo group who required rescue antiemetic revealed that 2 of 7 (28.6%) patients who received ondansetron, 3 of 14 (21.4%) patients who received promethazine, and 1 of 10 (10%) patients who received droperidol required unblinding and administration of a second antiemetic. Statistical power was insufficient to reach significance among the groups (p = 0.613).  
Because of the small sample size, the authors were unable to show statistically significant difference in efficacy among droperidol, promethazine, and ondansetron. |
Women aged 18 – 40 years (N = 295)  
Premedication:  
1. atropine 0.6 mg  
2. atropine 0.6 mg + diazepam 10 mg  
3. atropine 0.6 mg + promethazine 50 mg | Promethazine significantly reduced nausea and vomiting from 6% in group 1. to 1% in group 3. (p-value not stated).  
Premedication with promethazine is advocated for better recovery outcome. |
Women aged between 44.0 ± 10.2 and 47.0 ± 5.2 years (N = 90)  
1. Pregroup - received promethazine 0.1 mg/kg infusion before anesthesia induction  
2. Postgroup - received promethazine 0.1 mg/kg infusion at the end of surgery  
3. Control group - received normal saline | There were significant differences regarding nausea, vomiting, and patients who asked for antiemetic at the first 0-6 h and 0-24 h after surgery between group 3. and groups 1. and 2. (p < 0.05).  
During the first 0-6 h:  
- 42% of patients in group 3. were nauseous compared to 17% in groups 1. and 2. (p < 0.05).  
- 29% of patients in group 3. vomited compared to 7% in groups 1. and 2. (p < 0.05).  
- 22% of patients in group 3. asked for rescue antiemetic compared to 3% in group 1. and 7% in group 2. (p < 0.05).  
During the 0-24 h:  
- 47% of patients in group 3. were nauseous compared to 21% in group 1. and 23% in group 2. (p < 0.05).  
- 32% of patients in group 3. vomited compared to 10% in group 1. and 7% in group 2. (p < 0.05).  
- 22% of patients in group 3. asked for rescue |
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<td>14.</td>
<td>Moser (2006) [26] Prospective study (nonrandomized) Adults aged 27 – 81 years (N = 87) 1. promethazine 6.25 mg or 12.5 mg i.v. 2. ondansetron 4 mg i.v.</td>
<td>For patients who received promethazine 6.25 or 12.5 mg, nausea and vomiting were relieved at 1 hour in 74% and 68%, respectively, compared with 59% in group 2. Results at 3 hours were 67% and 80% for group 1 and 71% for group 2. No differences were significant (p-values not stated). In patients requiring treatment for nausea and/or vomiting from any cause except chemotherapy or pregnancy, promethazine was as effective as ondansetron.</td>
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<td>15.</td>
<td>Habib (2005) [27] Retrospective review (not randomized) Adults aged 18 – 65 years (N = 431) Rescue antiemetic in PACU: 1. ondansetron 4 mg 2. droperidol 0.625 to 1.25 mg 3. metoclopramide 10 mg 4. promethazine 6.25 to 25 mg 5. dimenhydrinate 25 to 50 mg</td>
<td>In patients who failed prophylaxis with ondansetron, the complete response rate (no nausea, no emesis, no need for further rescue) after rescue with promethazine 6.25 to 25 mg (78%) was significantly higher compared with a second dose of ondansetron (46%; p = 0.02; OR 0.21; 95% CI 0.07-0.63). In patients who failed prophylaxis with droperidol, the complete response rate was significantly higher after rescue with promethazine 6.25 to 25 mg (77%; p = 0.02; OR 0.38; 95% CI 0.18-0.84) and dimenhydrinate (78%; P = 0.04) compared with a second dose of droperidol (56%). An antiemetic acting at a receptor different from the site of action of the medicine used for PONV prophylaxis should be considered for the treatment of established PONV because it might be more efficacious compared with a repeat dose of the same medicine used for prophylaxis.</td>
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<td>16.</td>
<td>Nale (2007) [29] Double-blind RCT Adults aged 16 – 80 years (N = 120). Oral premedication 1 hour prior surgery and subsequent at 8 hour intervals for total 24 hours: 1. shaving of fresh ginger 250 mg 2. metoclopramide 10 mg 3. prochlorperazine 5 mg 4. promethazine 20 mg 5. ondansetron 4 mg 6. placebo</td>
<td>The incidence of PONV: 1. shaving of fresh ginger 15%; 2. metoclopramide 40%; 3. Prochlorperazine 35%; 4. promethazine 20%; 5. ondansetron 25%; 6. placebo 45%. The frequency and quantity of PONV was significantly lower with ginger group than control. The incidence of nausea was considerably less with promethazine (5%) then in control group (10%) (p value not reported). P-values obtained by statistical analysis and comparison of used drugs to placebo, or among themselves were not reported.</td>
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<td>17.</td>
<td>Habib (2007) [30] Retrospective review (not randomized) Adults aged &gt; 18 years Patients (N = 18209) initially received PONV prophylaxis with ondansetron 4 mg.</td>
<td>In patients with established PONV who failed ondansetron prophylaxis and needed rescue antiemetic treatment, the response rate (no nausea, no emesis, no need for further rescue) was significantly higher after promethazine (68%) than after repeat dose of ondansetron (50%; p &lt; 0.0001).</td>
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Rescue antiemetic administered in PACU within 4 hours after PONV prophylaxis (N = 3814):
1. ondansetron 4 mg
2. promethazine 6,25; 12,5 or 25 mg

There was no difference in efficacy between 6.25 mg and higher doses of promethazine for the treatment of established PONV in those patients p = 0.3).

18. **Pellegrini (2009)** [31]  
**RCT**  
Adults aged between 33.98 ± 10.9 and 37.09 ± 11.0 years (N = 85)  
Patients received PONV prophylaxis with ondansetron 4 mg.  
Rescue (PONV) treatment with:
1. inhaled 70% isopropyl alcohol (IPA)  
2. promethazine 12,5 to 25 mg i.v.

The overall incidence of postoperative nausea was 76% in group 1. and 60% in group 2. (p = 0,119). The incidence of PONV following discharge home was significantly higher in group 1. (P = 0,019). No differences in verbal numeric rating scale (VNRS) scores were noted between groups on initial complaint of nausea. A significantly faster time to a 50% reduction in VNRS scores was noted in group 1. compared with group 2. in the postanesthesia care unit (P = 0,045), same-day surgery unit (P = 0,032), and the home (P = 0,017) settings. Satisfaction with nausea control was similar between groups.

IPA is as effective in treating PONV as promethazine in patients who have been identified as high risk for PONV.

**Double-blind RCT**  
Women aged between 32.8 ± 7.2 and 34.3 ± 8.3 years (N = 138)  
15 min before the end of surgery i.v. and than 12 h after surgery for five oral doses, patients received:
1. granisetron 0.1 mg i.v. (1 mg oral)  
2. promethazine 6.25 mg i.v. (12.5 mg oral)  
3. granisetron + promethazine (combination, same doses as above)

Patients in the combination group had a significantly higher cumulative total response rate (no vomiting/retching, no more than mild nausea, no use of rescue antiemetic) at 24 h after surgery compared with promethazine group; combination 70%, promethazine 36%, P = 0,0079. The combination group was superior to promethazine group at 6 (p < 0.013), 24 (p = 0.008), 48 (p = 0.004), and 72 (p = 0.004) hours after surgery.

The maximum nausea scores from 6 to 72 h after surgery were significantly lower in the combination group than in the promethazine group (p < 0.01).

The incidence of nausea, vomiting, and use of rescue antiemetic was lower in the combination group but the difference did not reach statistical significance (p-value not stated).

There was no difference between groups in satisfaction with PONV management (p-value not stated).

Combination of granisetron and promethazine is more effective in reducing PONV and PDNV than promethazine monotherapy.

<table>
<thead>
<tr>
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<tr>
<td>01.</td>
<td>Tramèr (1999) [33]</td>
<td>The addition of promethazine to</td>
<td>Promethazine showed showed promising</td>
</tr>
<tr>
<td>No.</td>
<td>Article; Methodology</td>
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</tr>
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</table>
| 02. | **Fujii (2005)** [34]  
MEDLINE and EMBASE search (Jan 1990 – Oct 2003) was conducted.  
Included two studies with promethazine [21], [22]  
Over the 24-h period, the incidence of PONV was significantly reduced in promethazine group and combination group of promethazine and ondansetron compared with placebo group and ondansetron group. [21]  
There was no difference between the placebo and promethazine groups in the worst level of nausea reported, the incidence of nausea of any severity, moderate to severe nausea, vomiting, or the need for rescue antiemetics following discharge. [22]  
Among traditional antiemetics (e.g., anticholinergics, antihistamines, phenothiazines, butyrophenones, and benzamide), dimenhydrinate and perphenazine are highly efficacious for the prophylaxis against PONV following laparoscopic cholecystectomy. | |
| 03. | **Carlisle (2006)** [35]  
Cochrane systematic review  
The Cochrane Central Register of Controlled Trials (Jan 1966 - May 2004), EMBASE (Jan 1985 - May 2004), CINAHL (1982 - May 2004), ISI WOS (to May 2004), Lilac, and Ingenta searches were conducted.  
Included 7 clinical trials from Table 1. evaluating the effectiveness of promethazine: [21], [22], [13], [19], [15], [20], [18]  
Compared to placebo, the risk (95% confidence interval) for PONV is decreased by promethazine 0,46 (0,25 to 0,82), but there was no evidence that the risk of postoperative vomiting is changed by promethazine 0,76 (0,40 to 1,45).  
Compared to no treatment, there was no evidence that promethazine changes the risk of postoperative nausea – relative risk 0,81 (0,55 to 1,20), or the risk of postoperative vomiting – relative risk 0,53 (0,15 to 1,84).  
Eight medicines (droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron) were identified that reliably prevented nausea or vomiting after surgery.  
There was no reliable evidence that one medicine was better than another. | |
| 04. | **Fujii (2008)** [36]  
MEDLINE and EMBASE searches from Jan 1990 to Dec 2007 were conducted.  
Included one study with promethazine [21]  
Over the 24-h period, the incidence of PONV was significantly reduced in promethazine group and combination group of promethazine and ondansetron compared with placebo group.  
There was no difference between placebo and ondansetron groups.  
Combination of antiemetic therapy with an antiserotonin (ondansetron, granisetron) plus traditional antiemetics (promethazine, droperidol) or dexamethasone is highly effective for the prophylaxis against PONV. | |

**Summary of results**

Retrieved clinical trials and systematic reviews evaluating the effectiveness of promethazine for the management of postoperative nausea and vomiting are presented in Tables 1. and 2.
Nineteen relevant clinical trials published between 1977 and 2009 were identified. The majority of them (12/19; 63.2%) were double-blind RCTs, 3 were RCTs, and 4 articles presented nonrandomized prospective or retrospective studies. The quality of data collection was operator-dependent and in some aspects, like the evaluation of severity of nausea, may be inaccurate or underreported. Objective evaluation of severity of nausea is very difficult and “there may be as many scales for assessing nausea/vomiting as there are investigative groups studying the phenomenon”. [37] Four clinical trials used validated visual analogue (VAS) or verbal rating (VRS) scales to assess nausea with “0” representing no nausea and “10” representing worst possible nausea, in seven clinical trials the severity was not assessed or it was unclear how the assessment was done, and the others eight reported using a scoring systems which were not validated, and were not reported again in other articles. Additional limitations are the low or limited number of patients available for analysis, the recruitment of only women, and the non-existence of placebo groups in some studies. The limitation of some nonrandomized studies was the choice of antiemetic medicines, which was left at discretion of attending anesthesiologist. However, those clinical trials evaluated the effectiveness of promethazine in 6486 patients of which 6299 were adults aged 16 or more, and 100 were children. One clinical trial included 87 patients aged 13 – 72 years, but we were unable to identify the exact number of participants that were under or over 16 years from the published data. [21] Promethazine was used in different dosages and administered using the different routes of administration (oral, intramuscular, intravenous, combined intramuscular + intravenous) across the studies. The use of different dosages may have led to different effects. The doses of promethazine were determined in three ways. In 12 studies, the dose of promethazine was fixed and ranged from 6,25 mg to 50 mg. In 5 studies, the dose of promethazine was calculated according to patient’s body weight. Each of these studies used different dosing regimes, with doses ranging from 0,1 mg/kg to 1 mg/kg. In one study, promethazine was added to morphine as part of patient-controlled analgesia regimen and the patient was administered on average 17,6 mg of promethazine over a 24-h period.

Due to the heterogeneity of the retrieved clinical trials, it was not possible to pool the data in a meta-analysis as no common or unique outcome could be determined. In order to analyze the effect of promethazine as precisely as possible, the outcomes of retrieved clinical trials presented in Table 1. are reported by the intervention used. Six different groups were identified:

1) Promethazine vs. placebo
In seven clinical trials [16, 18, 20-22, 24, 25], promethazine was compared to placebo. In 5 of them participated only women (N = 989; aged 18 – 55 years), one trial was with adults (N = 120) aged 18 – 40 years, and one trial included 87 patients aged 13 – 72 years. Promethazine was found effective in reducing the occurrence of PONV in 5 articles, while 2 studies found him ineffective for antiemetic prophylaxis.

2) Promethazine vs. another antiemetic medicine
In three clinical trials [13, 26, 29], promethazine was compared to other antiemetic medicine. One study with children (N = 100) aged 2 – 10 years reported that promethazine reduced the incidence of postoperative vomiting when compared to droperidol, and the other with adults (N = 87) aged 27 – 81 years found promethazine as effective as ondansetron. The third study with patients aged 16 – 80 years (N = 120) found that shaving of fresh ginger decreased the incidence of PONV significantly when compared to placebo. Same study also evaluated the effect of promethazine and found that the incidence of nausea was considerably less with promethazine then in control group.

3) Promethazine + another antiemetic vs. placebo or the same antiemetic alone
In three clinical trials [19, 21, 32], combination of promethazine with another antiemetic was compared to placebo or to those same antiemetics administered alone. The study with 87 patients aged 13 – 72 years reported that combination of promethazine with ondansetron reduced the incidence of nausea, vomiting and combination of nausea and vomiting when compared with placebo. Same study also reported combination of promethazine and ondansetron to be more
effective in reducing the incidence of vomiting and combined nausea and vomiting than promethazine or ondansetron alone. The second study with women (N = 138) aged 32.8 ± 7.2 and 34.3 ± 8.3 years reported combination of granisetron and promethazine more effective in reducing PONV than promethazine monotherapy. The third study with adults (N = 60) aged 50 – 83 years also reported combination of medicines to be the most effective. In this study, oral promethazine was combined with transdermal scopolamine patch, and it was found that this combination is more effective in reducing incidence of PONV than promethazine monotherapy.

4) Promethazine in combination with morphine

In two clinical trials [14, 17], the effect of promethazine and morphine combination on incidence of nausea was tested. Both studies, one with adults (N = 270) aged 18 – 70 years and the other with women (N = 30) aged 18 – 60 years found that the use of promethazine had no effect on incidence of nausea. However, the later study reported that the use of promethazine as a adjunct to morphine was associated with a decrease in the symptom-therapy score for nausea.

5) Promethazine as a rescue antiemetic (2nd line treatment) vs. other antiemetics

In four clinical trials [23, 27, 30, 31], promethazine was used as a rescue antiemetic and was compared to other antiemetics. Adults (N = 4361) participated in these trials. In two studies (N = 116) the difference between promethazine and other used medicine was not revealed. Other two studies (N = 4245) found promethazine to be more efficient in reducing PONV than the repeated dose of the same antiemetic used for prophylaxis.

6) Promethazine vs. lorazepam

One clinical trial [15] with women (N = 124) aged 16 – 70 years compared promethazine to sedative (lorazepam). Primary outcome of this trial was to compare their effects as premedicants. However, it was also found that there is no difference among them in respect of late PONV.

Four systematic reviews published between 1999 and 2008 were identified. Two systematic reviews [33, 34, 36] included only one clinical trial evaluating the efficacy of promethazine in management of PONV. In one of them, it is stated that promethazine showed promising results in preventing nausea but due to limited number of patients the recommendation hadn’t been made. The second review recommended combination of antiserotonin plus traditional antiemetics (this includes promethazine) as highly effective for prophylaxis against PONV. The third review [34] included two clinical trials with promethazine. Among conclusions of this review, promethazine was not explicitly stated. The review which included the most clinical trials evaluating the effectiveness of promethazine was Cochrane systematic review.[35] The objective of that review was to assess the prevention of postoperative nausea and vomiting by different medicines and to compare their efficacies. In order to achieve that, 737 randomized controlled trials involving 103 237 people that compared a medicine with placebo or another medicine were included. Out of that, 7 clinical trials involving 618 people evaluated the effectiveness of promethazine. It was found that eight medicines reliably prevented nausea or vomiting after surgery: droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron. Those medicines prevented nausea or vomiting in three or four people out of every 10 who would have vomited or felt nauseated with a placebo. The authors did not find reliable evidence that one medicine was better than another. Side effects were mild. Concerning promethazine, there was no evidence that the risk of postoperative vomiting is changed by promethazine. Also, compared to no treatment, there was no evidence that promethazine changes the risk of postoperative nausea or the risk of postoperative vomiting.

Preoperative medication and sedation for short-term procedures

Anesthesia gives a surgeon possibility to operate under optimal conditions, and enables a patient to tolerate necessary procedures in a safe manner and without experiencing unbearable pain. Very often, the surgery is performed in general anesthesia. However, general anesthesia may not always be the best choice. Sometimes, local or regional anesthesia is more appropriate. The decision is
based on patient’s medical and surgical history, his/her physical examination, type of surgery, and patient's attitude and affect.

Premedication should be the first stage of anesthesia process and is conducted in the surgical ward or in a preoperative room. The aim is to make the process of anesthesia smooth, to reduce patient’s preoperative stress and anxiety, and to have a calm patient arriving in the operating room.

Procedural sedation or sedation for short-term procedures is the administration of sedative or other medicines (e.g. dissociative agents, anxiolytics) combined with or without analgesia. The aim of sedation is to induce a depressed level of consciousness that allows the patient to tolerate an unpleasant diagnostic or therapeutic procedure while maintaining airway control and cardiorespiratory function.

In WHO Model Formulary 2008, medicines recommended for use for preoperative medication and sedation for short-term procedures are: atropine, diazepam, promethazine, and morphine. [3]

After a literature search and analysis of retrieved papers, 17 relevant clinical trials and 1 systematic review were identified that evaluated the effectiveness of promethazine as a preoperative medication and sedative for short-term procedures (Table 3., Table 4.).

Table 3. Clinical trials evaluating the effectiveness of promethazine as a preoperative medication and sedative for short-term procedures

<table>
<thead>
<tr>
<th>No.</th>
<th>Article; Study Type; Study Design</th>
<th>Findings; Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.</td>
<td>Conner (1977) Double-blind RCT</td>
<td>In the response categories (relief of anxiety, sedation, and patient acceptance) three medicine combinations (morphine 5 mg or 10 mg + promethazine 12.5 mg, and morphine 5 mg + promethazine 25 mg) produced the highest mean scores, and there were no significant differences between them (p-values not stated). The mean score of the morphine 5 mg + promethazine 12.5 mg combination was significantly better than that with the lower promethazine dose of 6.25 mg combination in all of the variables measured (p-value not stated). Promethazine improved relief of anxiety, sedation, and patient acceptance when added to morphine.</td>
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<tr>
<td></td>
<td>Adults aged 18 – 70 years (N = 270)</td>
<td>One hour before surgery, patients received morphine 5 mg or 10 mg alone or in combination with promethazine 6.25, 12.5, or 25 mg. Promethazine 25 mg alone also was studied.</td>
</tr>
<tr>
<td></td>
<td>Double-blind RCT</td>
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<td></td>
<td>Women aged 16 – 70 years (N = 124)</td>
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<tr>
<td></td>
<td>As premedication, 2-3 hours before surgery: 1. lorazepam 2.5 mg p.o. 2. promethazine 50 mg p.o.</td>
<td>Both premedications were equally effective in providing subjective relief from anxiety (p-values not stated). In the anesthetic room, 30% of group 1. and 23% of group 2. considered their anxiety less. After operation 79% patients in group 1. and 77% in group 2. considered that the premedication had produced good relief of anxiety. Concerning sedation, 7 patients in group 1. and 3 patients in group 2. said they did not sleep before transport to the operating room (the percentages and p-values were not stated). Significantly higher amnesic effect of lorazepam (p-value not stated). Neither promethazine nor lorazepam fulfil the requirements of the ideal premedicant, but both can provide relief of anxiety and sedation.</td>
</tr>
<tr>
<td>02.</td>
<td>Dodson (1978) Double-blind RCT</td>
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<tr>
<td></td>
<td>Women aged 16 – 70 years (N = 124)</td>
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<tr>
<td>03.</td>
<td>Desjardins (1981)</td>
<td>No significant difference in the quality of induction of</td>
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<tr>
<td>No.</td>
<td>Article; Study Type; Study Design</td>
<td>Findings; Conclusion</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>Double-blind RCT</td>
<td>Children aged 1-12 years (N = 156)</td>
</tr>
<tr>
<td>04.</td>
<td>Vella (1985) [16] Double-blind RCT</td>
<td>Women (N = 477).</td>
</tr>
<tr>
<td>05.</td>
<td>Adam (1986) [39] Double-blind balanced order study</td>
<td>Adults aged 45 – 70 years (N = 12; 9 F+3 M)</td>
</tr>
<tr>
<td>No.</td>
<td>Article; Study Type; Study Design</td>
<td>Findings; Conclusion</td>
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</table>
| 06. | **Jalbout (1994) [40]**  
Double-blind RCT  
Adults aged 18 – 65 years (N = 98)  
Half an hour before transfer to the operating room, patients received premedication i.m.:  
1. **midazolam** 7.5 mg  
2. **promethazine** 25 mg  
3. **droperidol** 2.5 mg  
4. **placebo**  
| Level of anxiety was evaluated using a Beck Anxiety Inventory (BAI). Droperidol produced a decrease in the BAI score in 12% of patients, placebo in 25%, promethazine in 55%, and midazolam in 83.3%.  
Significantly more patients who received midazolam had a decrease in their anxiety state compared to promethazine (p < 0.001), droperidol (p < 0.005), and placebo (p < 0.005), while placebo was superior to droperidol (p-value not stated).  
Midazolam is a better anxiolytic medicine than all other tested. |
| 07. | **Sandhya (1994) [18]**  
RCT  
Women aged between 22.4 ± 2.5 and 25.0 ± 4.88 years (N = 32)  
Patients received pentazocine 0.6 mg/kg i.v. 5 minutes before induction of anesthesia along with either:  
1. **isotonic saline** (Control group)  
2. **promethazine** 0.5 mg/kg  
3. **metoclopramide** 0.2 mg/kg  
| Sedation was scored at the end of anesthesia (t1), 1 hour later (t2) and at the time of discharge (t3). The scores were comparable, not significantly different (p-values not stated).  
In group 1, sedation score was at t1 2,27; at t2 3,82; and at t3 4,00.  
In group 2, the scores were 2,55; 3,45; and 4,00, in group 3, 2,10; 3,90; 4,00, respectively. |
| 08. | **Ong (1996) [41]**  
Double-blind RCT  
Children aged 1 – 5 years (N = 146)  
Patients received premedication orally about 2 hours before scheduled surgery:  
1. **chloral hydrate** 40 mg/kg (max. 1 g)  
2. **midazolam** 0.2 mg/kg  
3. **promethazine** 1 mg/kg  
4. **trimeprazine** 3 mg/kg  
5. **placebo**  
| Assessed by the anesthetist, sedation at time of induction was considered adequate in more than 50% of the children in the group 1. and group 4.  
Promethazine induced adequate sedation in 39,1% of the children.  
At 2 out of 6 stages of assessment, significantly different outcomes concerning promethazine were found. At those 2 stages, more children who were crying / anxious were in promethazine group.  
The children benefited from some sedative premedication and the chloral hydrate and trimeprazine gave the best sedation at induction. The effect of trimeprazine extended longer into the postoperative period. |
| 09. | **Irjala (1996) [42]**  
Double-blind RCT  
Adults aged between 34 ± 13 and 41 ± 12 years (N = 57)  
Preceding evening and 1.5-2 hours prior to scheduled surgery, patients received orally:  
1. **promethazine** 25 mg  
2. **ranitidine** 150 mg  
3. **promethazine** 25 mg + **ranitidine** 150 mg  
4. **placebo**  
| Patient assessed the quality of sleep with the aid of visual analogue scale (VAS). There was no significant difference between the groups in the assessment of the quality of the preoperative night's sleep (p = 0.9).  
The general effectiveness of the study medications as hypnotics was ranked as equal by the patients (p = 0.8).  
H1 or combined H1/H2 blockade did not differ from placebo pretreatment in the various biochemical and clinical indicators of preoperative stress. |
| 10. | **Parlow (1999) [22]**  
Double-blind RCT  
Women aged 35 ± 9 years (N = 95)  
<p>| The incidence of excessive drowsiness was significantly higher in patients receiving promethazine on arrival home (33 vs 20% for placebo, P = 0,001), and at bedtime (41 vs 6% for placebo, P &lt; 0,001). |</p>
<table>
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</table>
Children aged 3 – 9 years (N = 90)  
Premedication administered orally:  
1. midazolam 0.5 mg/kg  
2. triclofos 70 mg/kg  
3. promethazine 1.2 mg/kg  
Patients were placed to a calm room until the sedative effects of premedication started to appear.  
Sedative scores “best” for group 1. (4.70 ± 0.12), followed by groups 2. (4.93 ± 0.11) and 3. (5.27 ± 0.09). The difference was highly significant between groups 1 and 3 (P < 0.001), and significant between groups 2 and 3 (P < 0.05).  
The recovery from sedation was most rapid for group 1. (92.88 ± 2.53 minutes) and slowest for group 3. (142.67 ± 2.58 minutes). The difference between groups was significant (p < 0.001).  
Midazolam was found to be the best drug among the three to produce conscious sedation in children. Oral midazolam is suitable premedication for child patients during short dental procedures. | |
Women aged 18 – 40 years (N = 295).  
Premedication:  
1. atropine 0.6 mg  
2. atropine 0.6 mg + diazepam 10 mg  
3. atropine 0.6 mg + promethazine 50 mg  
Diazepam reduced the delirium (talkativeness and restlessness) during recovery from 15.4% in group 1. to 1.3%, but prolonged the recovery time from 45 ± 23.1 to 200 ± 53.4 minutes (P < 0.01). Promethazine significantly reduced delirium from 15.4% in group 1. to 2.9% (P < 0.01), but didn't prolong the recovery time significantly from 45 ± 23.1 to 70 ± 36.8 minutes.  
Premedication with promethazine is advocated for better recovery outcome. | |
Women aged between 44.0 ± 10.2 and 47.0 ± 5.2 years (N = 90)  
1. Pregroup - received promethazine 0.1 mg/kg infusion before anesthesia induction  
2. Postgroup - received promethazine 0.1 mg/kg infusion at the end of surgery  
3. Control group - received normal saline  
There was no difference between groups for sedation score.  
At 3 h after surgery, sedation score was 0.5 ± 0.2 in group 1.; 0.3 ± 0.2 in group 2.; and 0.5 ± 0.3 in group 3 (p = 0.243).  
At 6 h, sedation score was 0.1 ± 0.1 for all groups (p = 0.421).  
At 12 h, 24 h, and 48 h after surgery, sedation scores were 0 for all groups.  
Morphine consumption for the Control and Post groups was significantly higher than for the Pre group (p < 0.05) at 3, 6, 12, and 24 h postoperatively, but not at 48 h (p-value not stated).  
Preoperative administration of promethazine reduces postoperative morphine consumption compared with postoperative and placebo administration. | |
Adults aged 27 – 81 years (N = 87)  
Patients with nausea and/or vomiting from any cause were administered:  
1. promethazine 6.25 mg or 12.5 mg i.v.  
2. ondansetron 4 mg i.v.  
Median sedation scores at 1 h were 3.0 (fully awake = 4) for both groups.  
At 3 h the median sedation score was 4.0 in group 1. and 3.5 in group 2. The difference was not significant (p > 0.05).  
The median ratings for low-dose Promethazine showed slightly less sedation at 1 and 3 h than ondansetron, but the differences were not significant (actual numbers and p-value not stated). | |
<table>
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<tbody>
<tr>
<td>15.</td>
<td>Habib (2007) [30] Retrospective review (not randomized) Adults aged &gt; 18 years</td>
<td>In patients with nausea and/or vomiting from any cause, there was no significant difference in sedation ratings between the intravenous promethazine dosages, and between promethazine and ondansetron.</td>
</tr>
<tr>
<td>16.</td>
<td>Braude (2008) [44] Double-blind RCT Adults aged 18 – 65 years (N = 120)</td>
<td>Anxiety visual analog scale (VAS) scores at 30 min after medicine administration decreased in both groups without significant difference between the two groups (p = 0.828). Sedation VAS scores at 30 min after medicine administration increased in both groups (5 mm in group 1. and 19 mm in group 2.). There is a significantly greater increase in sedation among patients in promethazine group (difference 14 mm; 95% CI = 5 – 24 mm; p = 0.005). Promethazine is associated with greater sedation compared to ondansetron.</td>
</tr>
<tr>
<td>17.</td>
<td>Gan (2009) [32] Double-blind RCT Women aged between 32.8 ± 7.2 and 34.3 ± 8.3 years (N = 138) 15 min before the end of surgery i.v. and than 12 h after surgery for five oral doses, patients received: 1. <strong>granisetron</strong> 0.1 mg i.v. (1 mg oral) 2. <strong>promethazine</strong> 6.25 mg i.v. (12.5 mg oral) 3. <strong>granisetron</strong> + <strong>promethazine</strong> (combination, same doses as above)</td>
<td>There were no differences in the sedation scores between the groups at discharge from postanesthesia care unit. Sedation score in group 1. was 4.7 ± 0.5; in group 2. 4.4 ± 0.7; and in group 3. 4.6 ± 0.5 (p-value not stated).</td>
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</tbody>
</table>
Table 4. Systematic review evaluating the effectiveness of promethazine as a preoperative medication and sedative for short-term procedures

<table>
<thead>
<tr>
<th>No.</th>
<th>Article; Methodology</th>
<th>Remarks / Results concerning promethazine role</th>
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<tbody>
<tr>
<td>01.</td>
<td>Matharu (2006) [45]</td>
<td>Midazolam, triclofos, and promethazine were evaluated. Midazolam was found to be the best medicine among the three to produce conscious sedation in children.</td>
<td>Authors were not able to reach any definitive conclusion on which was the most effective medicine or method of sedation used for anxious children.</td>
</tr>
</tbody>
</table>

**Summary of results**

Retrieved clinical trials and systematic review evaluating the effectiveness of promethazine as a preoperative medication and sedative for short-term procedures are presented in Tables 3. and 4.

Seventeen relevant clinical trials published between 1977 and 2009 were identified. The majority were double-blind RCTs (12/17; 70.5%), in one RCT blinding was not reported, and 4 articles presented nonrandomized prospective or retrospective studies. Seven clinical trials evaluated the effectiveness of promethazine in adults (N = 4458) aged 18 – 81 years, seven trials included only women (N = 1251) aged 16 – 70 years, and in three the subjects were the children aged 1 – 12 years (N = 392). In these studies, promethazine was usually administered shortly prior or after other medicines so it was difficult to precisely determine its actual effectiveness. Also, it was difficult to evaluate the severity of anxiety or the level of sedation. Six clinical trials used validated scales to assess anxiety or sedation such as Beck Anxiety Inventory, Visual Analogue Scale, or Ramsey score, but in the other 11 trials it was unclear how the assessment was done or they reported not validated scales. Therefore, the quality of data collection was partially operator-dependent and it may be inaccurate. Additional limitations were the low or limited number of patients available for analysis (8 studies involved less than 100 subjects), the recruitment of only women, and the non-existence of placebo groups in 7 studies. Promethazine was used in different dosages and administered using different routes of administration (oral, intramuscular, intravenous, combined intramuscular + intravenous) across the studies. The use of different dosages may have led to different effects. In 11 studies, the dose of promethazine was fixed and ranged from 6,25 mg to 50 mg. In 6 studies, the dose of promethazine was calculated according to patient’s body weight. Each of these studies used different dosing regimes, with doses ranging from 0,1 mg/kg to 1 mg/kg. Bearing in mind the heterogeneity of the retrieved clinical trials, it was not possible to identify a common or unique outcome and to pool the data in a meta-analysis. But, in order to analyze the effect of promethazine as precisely as possible, the trials presented in table 3. are reported by their primary outcome. Three different groups were identified:

1) Premedication: relief of anxiety and/or sedation

In nine clinical trials [14, 15, 24, 25, 38-41, 43], the primary outcome was to evaluate the effect of promethazine in premedication of the patients. Three studies involved adults aged 18 – 70 years (N = 380). In two of them, when added to morphine or compared to placebo, it was found that promethazine improved relief of anxiety and sedation. However, the third study which evaluated several anxiolytics, found midazolam to be better in reducing the level of anxiety than others tested. Three studies involved only women aged 16 – 70 years (N = 509). One study comparing
promethazine and lorazepam found both premedications equally effective in providing relief of anxiety and sedation. The other study compared promethazine and diazepam and found that both medicines significantly reduced talkativeness and restlessness during recovery time, but advocated premedication with promethazine because it didn’t prolong the recovery time. The last study compared promethazine to placebo and found no differences between groups for sedation score. In remaining three studies, the subjects were the children aged 1 – 12 years (N = 392). None of these three studies found promethazine more effective than other medicines. One study stated that the used premedications were not better than placebo, and the others recommended either midazolam or chloral hydrate and trimeprazine as the best.

2) Reduction of incidence of nausea and vomiting

In seven clinical trials [16, 18, 22, 26, 30, 32, 44], the primary outcome was to evaluate the effect of promethazine in reduction of incidence of nausea and vomiting. Four studies involved women (N = 742), and based on data reported the age ranged between 22.4 ± 2.5 and 35 ± 9 years. Out of these four, three studies included placebo group. In two of them promethazine induced more drowsiness, and the third study found no significant difference. Three studies also compared promethazine with another antiemetic. In one study promethazine caused more sedation then metoclopramide, but the second study found comparable sedation scores for these two antiemetics. The third study evaluated promethazine and granisetron and showed no difference in sedation scores. The remaining three studies involved adults aged 18 – 81 years (N = 4021). In all of them patients received promethazine and ondansetron for the treatment of nausea and/or vomiting or as a rescue antiemetic. One study (N = 87; age 27 – 81 years) found no significant difference in sedation ratings between them, but the other two found that promethazine is associated with greater sedation compared with ondansetron.

3) Effects of histamine blockade on preoperative stress indicators

One clinical trial [42] with adults (N = 57) aged between 34 ± 13 and 41 ± 12 years evaluated the use of H1 and H2 antagonist in preoperative treatment. Four groups of patients were established (promethazine, ranitidine, promethazine + ranitidine, and placebo), and there was no significant difference between the groups concerning their general effectiveness as hypnotics.

One systematic review evaluating the effectiveness of promethazine as a preoperative medication and sedative for short-term procedures was identified (Cochrane systematic review). [45] The objective of that review was to evaluate the efficacy of the various conscious sedation techniques in pediatric dentistry. In order to achieve that, 61 randomized controlled trials involving 3246 children up to 16 years of age comparing two or more medicines/techniques/placebo were included. Authors have reported that overall quality of studies was found to be disappointing with poor reporting often the main problem. Due to heterogeneity of the reported data, meta-analysis was not possible. Also, the variety of treatment regimens compared and different outcome measures made it difficult to isolate groups of studies that were sufficiently similar in design to allow sensible comparison. Therefore, authors were not able to reach any definitive conclusion on which was the most effective medicine or method of sedation used for anxious children. One double-blind RCT with promethazine not being part of mixture of medicines was included in this review. This study evaluated the effectiveness of midazolam, triclofos, and promethazine in 90 children aged 3 – 9 years. Midazolam was found to be the best medicine among the three to produce conscious sedation in children.

Summary of available safety data

Since its introduction in clinical practice and during the past decades, different phenothiazine derivates were used for premedication. They provided sedation, prevented nausea and vomiting, and had antihistaminic activity. Their use was accompanied with various side-effects, like respiratory depression, hypotension, extrapyramidal symptoms, thrombophlebitis, and allergic reactions. Promethazine is the only phenothiazine remaining for premedication.
Table 5. presents the side-effects of promethazine which were reported in clinical trials evaluating the effectiveness of promethazine for the management of postoperative nausea and vomiting, and in clinical trials evaluating the effectiveness of promethazine as a preoperative medication and sedative for short-term procedures (Tables 1. and 3.).

Table 5. Side-effects associated with the use of promethazine reported in clinical trials evaluated in this Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Article</th>
<th>Reported side-effects of promethazine</th>
</tr>
</thead>
</table>
| 01. | Dodson (1978) [15]  
Double-blind RCT  
Women aged 16 – 70 years (N = 124)  
Promethazine 50 mg p.o. was administered 2-3 hours before surgery (N = 71). | Among the patients who received promethazine:  
- 8 had nausea within 30 minutes after receiving the capsule  
- 6 had prolonged sedation, or dizziness, or dyskinetic side-effects, or depression, aggression, and confusion  
- 2 had diplopia  
- 1 had hallucinations, or heartburn |
| 02. | Desjardins (1981) [38]  
Double-blind RCT  
Children aged 1-12 years (N = 159)  
Promethazine 0.5 mg/kg was administered by mouth 1 hour before surgery. | Out of 40 patients who received promethazine, anesthetists’ observed:  
bradycardia and cardiac arrhythmias in 15% patients,  
sialorrhea in 10%, and tachycardia, laryngospasm, and bronchorrhea in 3%.  
Out of 38 patients who received promethazine, recovery room nurse’s observed:  
nausea and vomiting in 12% patients, sore throat and confusion in 10%, hypertension in 7%, and cough and inspiratory noise in 2%.  
Out of 35 patients who received promethazine, parent’s observed:  
Sore throat in 37% patients, cough in 29%, headache in 23%, difficulty to breathe in 20%, nausea and vomiting in 17%, hiccup, pyrexia, and drowsiness in 14%, nausea in 9%, dizziness and confusion in 6%, and myalgia in 3%. |
Double-blind RCT  
Children aged 2 – 10 years (N = 100)  
Promethazine was administered 0.5 mg/kg i.v. + 0.5 mg/kg i.m. (max. 25 mg) (N = 50) | Children treated with promethazine had a significantly (p < 0.001) higher incidence of restlessness (18 patients; 36%) compared to children treated with droperidol (4 patients; 8%).  
Other side-effects were not statistically different (p-values not reported).  
Among the patients who received promethazine, somnolence was present in 31 patients (62%), dry mouth in 8 patients (16%), disorientation in 3 patients (6%) and rash in 1 patient (2%). |
Double-blind RCT  
Adults aged 50 – 83 years (N = 60)  
For premedication the patients received oral promethazine 10 mg with or without transdermal scopolamine patch 1.5 mg (N = 40) | The incidence of pruritus, urinary retention and need for bladder catheterization was similar in all groups (p-values not reported).  
Out of 40 patients receiving promethazine, bladder catheterization was needed in 25 patients, and the pruritus was present in 20 patients. |
| 05. | Rodola (1995) [20]  
Double-blind RCT  
Adults aged 18 – 40 years (N = 120) | Patients receiving promethazine showed some degree of postoperative prolonged sedation, but this was not quantified and the actual numbers were not reported. |
Ten clinical trials reported side-effects after treatment with promethazine, but in general, promethazine was well tolerated. Out of those ten trials, 6 trials included adults (N = 536) aged 16 – 83 years. Promethazine was administered to 217 subjects. The sedation was the most commonly reported side-effect, and the others were dry mouth, dizziness, headache, hypotension, urinary retention, pruritus, and akathisia. Two trials with women (N = 219) aged 16 – 70 years reported side-effects after administering promethazine to 119 subjects. The prolonged sedation was also the most commonly reported side-effect in this group, and the others were nausea, dizziness, dyskinetic side-effects, depression, aggression, confusion, diplopia, hallucinations, and heartburn. Two trials (N = 259) evaluated the effect of promethazine in children aged 1 – 12 years (N = 90). In the first trial [38], promethazine 0.5 mg/kg (maximum dose not reported) was administered orally. Out of 40 patients, the side-effects were noticed in up to 37%. The most serious side-effects were noticed by the anesthetists’ and those were Bradycardia and cardiac arrhythmia in 15% patients. Tachycardia
and laryngospasm were observed in 3% patients. The most serious side-effect occurring at home and which were reported by the parents were difficulties with breathing in 20%, pyrexia, and drowsiness in 14% patients. Other side-effects were confusion, hypertension, hiccup, dizziness, and myalgia. As the most frequently reported were sore throat, cough, headache, nausea and vomiting. The second trial [13] included children (N = 50) to whom promethazine was administered intravenously and intramuscular with maximum dose being 25 mg. Children treated with promethazine had a significantly higher incidence of restlessness (18 patients; 36%) compared to children treated with droperidol. Other side-effects were not statistically different from those reported in droperidol group and were somnolence (31 patient; 62%), dry mouth (8 patients; 16%), disorientation (3 patients; 6%) and rash (1 patient; 2%).

**Risk of bias assessment**

Risk of bias in the included clinical studies was assessed by using The Cochrane Collaboration's risk of bias tool, which addresses the following domains: sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting and other issues. Information extracted from each report for the risk of bias tool is presented in the accompanying excel spreadsheet, along with a judgement of low, high or unclear risk of bias, as described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions version 5.0.2 (updated September 2009). The Cochrane Collaboration, 2009. Available from: [www.cochrane-handbook.org](http://www.cochrane-handbook.org). In the excel spreadsheet, “yes” designates a low risk of bias, and “no” designates a high risk of bias.

**Generation of allocation sequence**

Majority of studies (15 of 24) had unclear risk of bias with regard to generation of allocation sequence. In these studies, randomization was mentioned, but not properly described. In four studies (Khalil 1999, Parlow 1999, Chia 2004, Gan 2009) the method of randomization was explained. In three studies (Moser 2006, Habib 2005, Habib 2007) antiemetics were prescribed at the discretion of attending physicians and in one study (Adam 1986) a non-randomized “balanced order design” was used. Poor quality of one of the included studies (Nale 2007) raises concerns about how the randomization was conducted.

**Concealment of allocation sequence**

In 15 of 24 studies, there no attempt to conceal allocation sequence was reported. In three studies (Tarkilla 1995, Chia 2004, Gan 2009) the allocation concealment was properly done, and in another two studies (Desjardings 1981, Ong 1991) the allocation sequence was reportedly prepared by pharmacists not involved in study, but there was no explanation how the sequence was concealed from researchers. Four studies did not use randomization of subjects (Moser 2006, Habib 2005, Habib 2007, Adam 1986).

**Blinding**

Based on the statements in the study reports, we concluded that blinding of outcome assessors was done properly in 15 of 24 studies. Risk of bias with regard to blinding was judged to be unclear in all other studies. In six studies (Vella 1985, Sandhya 1994, Ikechebelu 2003, Moser 2006, Habib 2005, Habib 2007, Jalbout 1994), it was not clear who has done the outcome assessment or how the assessors were blinded. In two studies the blinding procedure was described, but unconvincing (Nale 2007, Adam 1986).

**Incomplete outcome data**

In majority of studies (17 of 24), risk of bias with regard to incomplete outcome data was low. Due to ambiguous reporting, the risk of bias was judged unclear in five studies (Silverman 1992, Chia 2004, Moser 2006, Habib 2005, Nale 2007). In one study (Vella 1985) a relatively high loss to
follow up was poorly explained, and in another one (Singh 2002) it was not clear how many subjects were in each of the study arms and only $P$-values were reported, without actual data.

**Selective outcome reporting**

We did not attempt to find protocols for the included studies, but we compared the outcomes stated in the methods section with the ones reported in the results section. An adequate match was found in 21 of 24 studies, which were thus judged to be under a low risk of bias with regard to selective outcome reporting. In two studies (Vella 1985, Silverman 1992) there was an outcome reported in the results, but not mentioned in the methods section, which was probably not associated with an increase in the risk of bias. In one study (Ikechebelu 2003), dizziness as an observed outcome was mentioned in the methods, but not reported in the results.

**Other potential threats to validity**

No sources of funding and no declaration of conflict of interest was reported in great majority of included studies – only two were reportedly sponsored by a pharmaceutical company (Gan 2009, Jalbout 1994). In some studies the number of patients was possibly too small to detect meaningful differences, although this relates more to lack of power and precision than to risk of bias. One study (Nale 2007) was very poorly reported and raised some serious concerns about the credibility of research.

**Conclusions**

Promethazine is listed as antiemetic medicines in the WHO Model Formulary 2008. It is evident from Tables 1. and 2. that despite its widespread use, little data evaluating the therapeutic efficacy of promethazine is available. There are more articles evaluating efficacy of other antiemetics, but evaluation of these treatments was beyond the scope of this review. Current guidelines do not recommend use of promethazine and metoclopramide in the treatment of PONV, nor as a part of pharmalogic combination for adults and children, nor as single medicine in children. [11] Recent Cochrane Database Systematic Review found that, compared to placebo, the risk for PONV is decreased by promethazine, but there was no evidence that the risk of postoperative vomiting is changed by promethazine. Also, compared to no treatment, there was no evidence that promethazine changes the risk of postoperative vomiting and postoperative nausea. [35] It is important to mention a “zero-tolerance” strategy proposal, in which the authors propose antiemetic algorithm for outpatients. [4] Promethazine is not recommended as a first-line medicine, but can be considered for use as a rescue antiemetic. Promethazine was deleted from the WHO Model List of Essential Medicines in 2009. There is no new data to indicate that it should be considered for re-instatement.

According to WHO Model List of Essential Medicines, promethazine is indicated to reduce a patient’s preoperative stress and anxiety, and as a sedative for short-term procedures. It is evident from Tables 3. and 4. that there is also little data available evaluating the effectiveness of promethazine as a preoperative medication and sedative for short-term procedures. The reason is that promethazine is no longer frequently used for these indications. Other medicines, such as midazolam, diazepam, propofol or ketamine are used more often, and there are more studies evaluating their efficacy as preoperative medications and sedatives. However, full evaluation of these treatments was beyond the scope of this review. Midazolam and propofol are the focus of other reviews that are currently being undertaken.

In conclusion, due to the limited amount of data to support its use as a preoperative medicine and sedative for short term procedures and the availability of more efficacious alternatives, it is recommended that promethazine should be deleted from section 1.3 of the WHO Model List of Essential Medicines.
References:


<table>
<thead>
<tr>
<th>Study</th>
<th>Generation of allocation sequence</th>
<th>Concealment of allocation</th>
<th>Outcomes</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
<th>No validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conner 1977</td>
<td>Study drugs were administered intravenously according to a randomized Latin Square sequence</td>
<td>unclear</td>
<td>not reported</td>
<td>unclear</td>
<td>drugs were administered by a physician, while assessment of outcomes was performed by a physician, not known to the investigators</td>
<td>yes</td>
</tr>
<tr>
<td>Dodson 1978</td>
<td>The order of administration of the drug was randomized</td>
<td>unclear</td>
<td>not reported</td>
<td>unclear</td>
<td>The coding of the capsules was not known by the investigators</td>
<td>yes</td>
</tr>
<tr>
<td>Vella 1985</td>
<td>The ampoules were &quot;randomly coded&quot;</td>
<td>unclear</td>
<td>not reported</td>
<td>unclear</td>
<td>not clear whether the drugs were administered by the same person who assessed the outcomes; the drug was administered in &quot;randomly coded ampoules&quot;, but there was a lot of mistakes and &quot;human failure&quot; reported in the study</td>
<td>unclear</td>
</tr>
<tr>
<td>Blanc 1991</td>
<td>Children were randomly assigned</td>
<td>unclear</td>
<td>not reported</td>
<td>unclear</td>
<td>Both treatments were administered in a double-blind fashion; outcomes were assessed by two trained nurses now aware</td>
<td>yes</td>
</tr>
<tr>
<td>Silverman 1992</td>
<td>Patients were assigned randomly to receive</td>
<td>unclear</td>
<td>not reported</td>
<td>unclear</td>
<td>The patients, Acute Pain Service physicians, and investigators were blinded to group assignment</td>
<td>yes</td>
</tr>
<tr>
<td>Sandhya 1994</td>
<td>The patients were divided randomly into three groups</td>
<td>unclear</td>
<td>not reported</td>
<td>unclear</td>
<td>Not clear who has done the outcome assessment, and whether the assessors were blinded</td>
<td>unclear</td>
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<td>Tarkkila 1995</td>
<td>Patients were prospectively randomised into three groups of equal size.</td>
<td>unclear</td>
<td>not reported</td>
<td>unclear</td>
<td>We had sixty blinded envelopes for premedication prepared by a trained nurse informed of</td>
<td>yes</td>
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<tr>
<td>Rodola 1999</td>
<td>Randomized study was carried out...</td>
<td>unclear</td>
<td>not reported</td>
<td>unclear</td>
<td>All patients were asked about PONV and kept under observation by an investigator not aware of the treatment each patient had</td>
<td>yes</td>
</tr>
<tr>
<td>Khalil 1999</td>
<td>Patients were randomly assigned to via random numbers table receive one of the following:</td>
<td>yes</td>
<td>not reported</td>
<td>unclear</td>
<td>Assessment was done by study blinded observers</td>
<td>yes</td>
</tr>
<tr>
<td>Parlow 1999</td>
<td>Subjects were randomised... according to a computer-generated randomization</td>
<td>yes</td>
<td>not reported</td>
<td>unclear</td>
<td>outcomes self-assessed by patients; the study was &quot;double blind&quot;</td>
<td>yes</td>
</tr>
<tr>
<td>Kreisler 2000</td>
<td>Patients were randomized...</td>
<td>unclear</td>
<td>not reported</td>
<td>unclear</td>
<td>Dizziness and nausea assessed by a blinded nurse</td>
<td>yes</td>
</tr>
<tr>
<td>Ikechbelu 2003</td>
<td>Patients were assigned randomly</td>
<td>unclear</td>
<td>not reported</td>
<td>unclear</td>
<td>not clear who assessed the outcomes and whether the</td>
<td>unclear</td>
</tr>
<tr>
<td>Chia 2004</td>
<td>Patients were randomly and equally divided into three groups, using a computer-generated table of random numbers</td>
<td>yes</td>
<td>not reported</td>
<td>unclear</td>
<td>An anaesthetiologist blinded to group allocation evaluated the patients</td>
<td>yes</td>
</tr>
<tr>
<td>Study</td>
<td>Generation of allocation sequence</td>
<td>Description</td>
<td>Judgement</td>
<td>Allocation of allocation</td>
<td>Description</td>
<td>Judgement</td>
</tr>
<tr>
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</tr>
<tr>
<td>Moser 2006</td>
<td>no randomization; the antiemetics were prescribed by the attending physicians at their discretion</td>
<td>no</td>
<td>no randomization</td>
<td>no</td>
<td>not clearly stated that nurses who assessed the patient outcomes were blinded</td>
<td>unclear</td>
</tr>
<tr>
<td>Habib 2005</td>
<td>non randomized; the choice of rescue antiemetic was at the discretion of the attending anestheziologist</td>
<td>no</td>
<td>no randomization</td>
<td>no</td>
<td>not clear who assessed the outcomes and whether the assessors were blinded</td>
<td>unclear</td>
</tr>
<tr>
<td>Nale 2007</td>
<td>Patients were randomly allocated to one of the six groups; number of patients in each group is exactly the same; the randomization was probably poorly</td>
<td>no</td>
<td>not reported</td>
<td>unclear</td>
<td>blinding procedure described, but not convincing, for example - &quot;all the drugs were powdered and filled in</td>
<td>unclear</td>
</tr>
<tr>
<td>Habib 2007</td>
<td>no randomization</td>
<td>no</td>
<td>no randomization</td>
<td>no</td>
<td>not clearly stated that nurses who assessed the patient outcomes were blinded</td>
<td>unclear</td>
</tr>
<tr>
<td>Gan 2009</td>
<td>Randomization was achieved using computer-generated codes</td>
<td>yes</td>
<td>group assignment was prepared in sealed opaque envelopes</td>
<td>yes</td>
<td>Intravenous and oral study medications were prepared by the hospital investigational drug service in syringes and gel capsules that looked identical. Dana were collected by research personnel who were blinded to the randomization and not involved with the clinical care of the</td>
<td>yes</td>
</tr>
<tr>
<td>Desjardins 1981</td>
<td>&quot;The hospital pharmacist assigned each patient at random to one of the four therapeutic groups&quot;</td>
<td>unclear</td>
<td>Allocation sequence made by the hospital pharmacists not involved in the study</td>
<td>yes</td>
<td>Identification of the drug was provided in the sealed envelope, to be used “in any emergency situations”; no such situations</td>
<td>yes</td>
</tr>
<tr>
<td>Adam 1986</td>
<td>&quot;Balanced order design&quot;</td>
<td>no</td>
<td>no randomization</td>
<td>no</td>
<td>Eventually all sleep records were coded, mixed in order and categorised “blind” for the different stages of sleep and wakefulness. The code was then</td>
<td>unclear</td>
</tr>
<tr>
<td>Jailbout 1994</td>
<td>&quot;randomized study&quot;</td>
<td>unclear</td>
<td>not reported</td>
<td>unclear</td>
<td>Outcome assessed by the investigators; design is claimed to be double-blind, but the method of blinding was not clearly</td>
<td>unclear</td>
</tr>
<tr>
<td>Ong 1996</td>
<td>&quot;Patients were randomized&quot;</td>
<td>unclear</td>
<td>The premedication drugs were labelled A to E and the</td>
<td>yes</td>
<td>All the observers were blinded to the identity of the given drugs</td>
<td>yes</td>
</tr>
<tr>
<td>Irjala 1996</td>
<td>&quot;randomized study&quot;</td>
<td>unclear</td>
<td>not reported</td>
<td>unclear</td>
<td>The study drugs were packed in individual envelopes and were given by nurses. The investigator in the operating unit was unaware of the premedication the patient had received. Outcomes were</td>
<td>yes</td>
</tr>
<tr>
<td>Singh 2002</td>
<td>&quot;Patients were randomized&quot;</td>
<td>unclear</td>
<td>not reported</td>
<td>unclear</td>
<td>All agents were mixed with flavored juice to maintain uniformity of taste and keep the study blinded</td>
<td>yes</td>
</tr>
</tbody>
</table>