Non-cosmetic breast surgery 2006

Summary recommendations

PROSPECT Breast Surgery Subgroup

For each review, a Subgroup of the **prospect** Working Group performs an initial evaluation of the evidence and also drafts clinical practice statements and recommendations, which are then discussed by the whole Working Group before a final consensus is reached. The Subgroup may sometimes include a non-Working Group member, to provide additional expertise in the procedure being reviewed.

For the breast surgery review, the Subgroup members were:

- Professor Francis Bonnet (PROSPECT Working Group member)
- Professor Frederic Camu (PROSPECT Working Group member)
- Dr Emmanuel Barranger (Service de Gynecologue-Obstétrique, Hopital Lariboisiere, Paris)

Grades of Recommendation

Recommendations are graded according to the overall level of evidence (LoE) on which the recommendations are based, which is determined by the quality and source of evidence (Appendix A: Levels of evidence and grades of recommendation).

Summary recommendations

PROSPECT provides clinicians with supporting arguments for and against the use of various interventions in postoperative pain based on published evidence and expert opinion. Clinicians must make judgements based upon the clinical circumstances and local regulations. At all times, local prescribing information for the drugs referred to must be consulted.

Pre-, intra- and postoperative interventions have been evaluated for the management of postoperative pain following breast surgery. Unless otherwise stated, ‘pre-operative’ refers to interventions applied before surgical incision, ‘intra-operative’ refers to interventions applied after incision and before wound closure, ‘postoperative’ refers to interventions applied at or after wound closure.

The following peri-operative interventions for breast surgery have been reviewed:

Pre-operative analgesic recommendations for breast surgery*

	Major breast surgery	Minor breast surgery
Pre-operative recommended	– Paravertebral block (Grade A) – Gabapentinoids (Grade A) – COX-2-selective inhibitors (Grade D)/paracetamol (Grade B) in short breast surgery procedures to provide sufficient analgesia in the early recovery period	– COX-2-selective inhibitors (Grade D)/paracetamol (Grade B) in short breast surgery procedures to provide sufficient analgesia in the early recovery period

Intra-operative analgesic recommendations for breast surgery

	Major breast surgery	Minor breast surgery
Intra-operative recommended	– n/a	– n/a

Postoperative analgesic recommendations for breast surgery

	Major breast surgery	Minor breast surgery
Postoperative recommended	– Conventional NSAID (Grade A) or COX-2-selective inhibitor (Grade B) – Strong opioid, titrated to effect (for high intensity pain) (Grade B) or weak opioids for moderate- to low-intensity pain (Grade B) – Paracetamol alone or in combination with other non-opioid analgesics (Grade B) for low-moderate intensity pain – Paracetamol in combination with opioid analgesics (Grade D) for high intensity pain	– Conventional NSAID (Grade A) or COX-2-selective inhibitor (Grade B) – Weak opioids for moderate- to low-intensity pain (Grade B) – Paracetamol alone or in combination with other non-opioid analgesics (Grade B) for low-moderate intensity pain – Paracetamol in combination with opioid analgesics (Grade D) for high intensity pain

*Appendix B: Descriptions of major, minor, and cosmetic breast surgery

Not recommended for breast surgery*

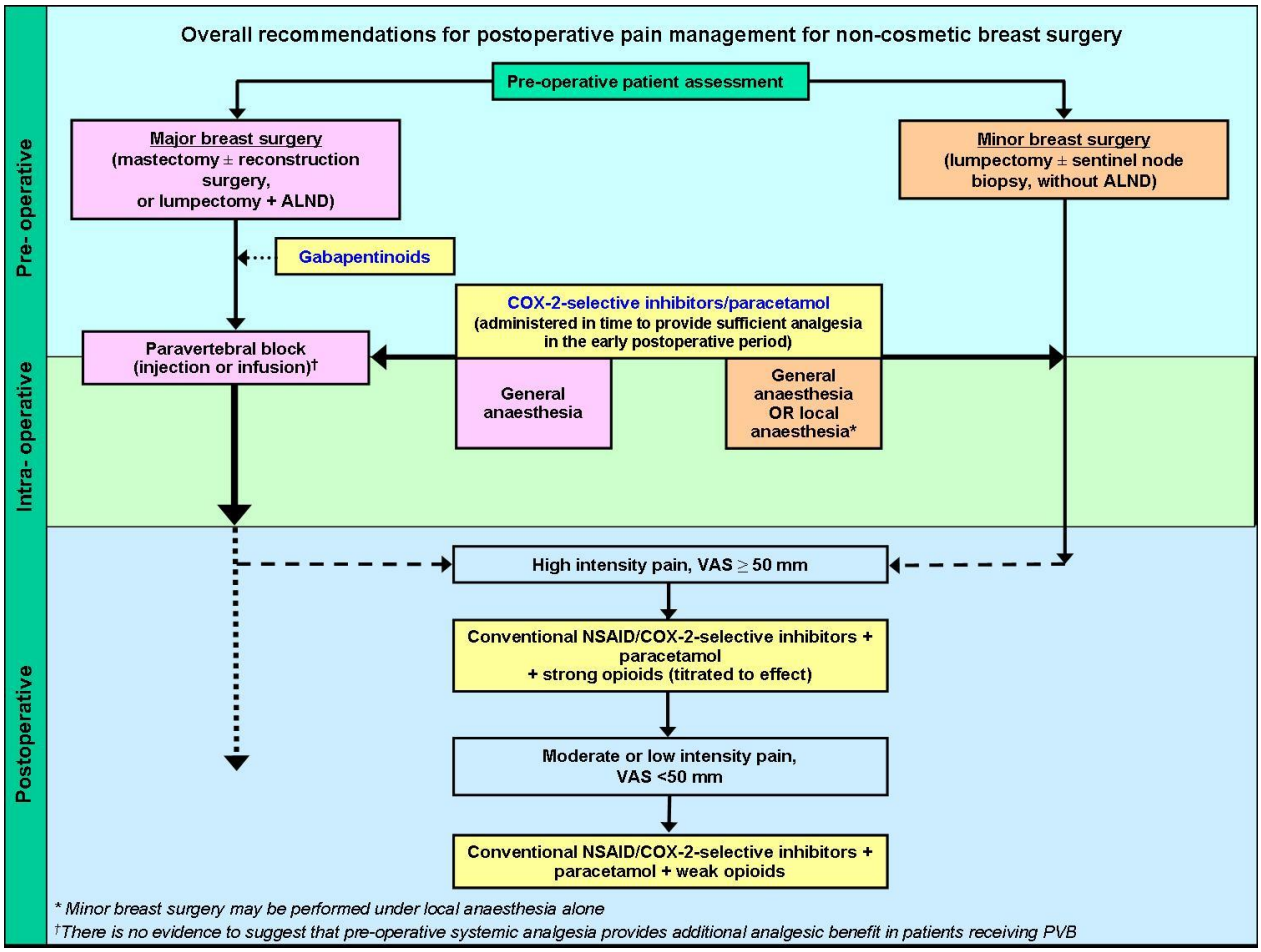
	Major breast surgery	Minor breast surgery
Pre-operative **not recommended**	– **Conventional NSAIDs** (Grade B) because of inconsistent procedure-specific and transferable evidence for benefit of pre- vs. postoperative administration, and increased risk of bleeding – **Corticosteroids for analgesia** (Grade D) due to insufficient procedure-specific evidence – **COX-2-selective inhibitors (except in short breast surgery procedures)** (Grade D) as transferable evidence shows inconsistent benefit of pre- vs. postoperative administration, and there is no procedure-specific evidence – *NMDA antagonists* ○ **Dextromethorphan** (Grade B) due to limited procedure-specific evidence ○ **Magnesium for analgesia** (Grade B) due to transferable evidence showing a lack of analgesic effects – **Paracetamol (except in short breast surgery procedures)** (Grade D) as there is no procedure-specific or transferable evidence to show whether pre-operative administration has any analgesic benefit compared with postoperative administration – **Strong opioids** (Grade D) due to no procedure-specific evidence of an analgesic benefit of pre- vs. postincisional administration – **Thoracic epidural analgesia** (Grade D) due to the risk of complications – **Electro-acupoint stimulation** (Grade D) due to limited procedure-specific and transferable evidence	– **Gabapentinoids** (Grade D) because pain intensity is commonly not severe enough to justify an adjuvant to the usual analgesic agents – **Conventional NSAIDs** (Grade D) because of inconsistent procedure-specific and transferable evidence for benefit of pre- vs. postoperative administration – **Corticosteroids for analgesia** (Grade D) due to insufficient procedure-specific evidence – **COX-2-selective inhibitors (except in short breast surgery procedures)** (Grade D) as transferable evidence shows inconsistent benefit of pre- vs. postoperative administration, and there is no procedure-specific evidence – *NMDA antagonists* ○ **Dextromethorphan** (Grade B) due to limited procedure-specific evidence ○ **Magnesium for analgesia** (Grade B) due to transferable evidence showing a lack of analgesic effects – **Paracetamol (except in short breast surgery procedures)** (Grade D) as there is no procedure-specific or transferable evidence to show whether pre-operative administration has any analgesic benefit compared with postoperative administration – **Strong opioids** (Grade D) due to no procedure-specific evidence of an analgesic benefit of pre- vs. postincisional administration – **Paravertebral block** (Grade D) because of the risk of complications – **Thoracic epidural analgesia** (Grade D) due to the risk of complications

		– **Electro-acupoint stimulation** (Grade D) due to limited procedure-specific and transferable evidence
Intra-operative **not recommended**	– **Corticosteroids for analgesia** (Grade D) due to insufficient procedure-specific evidence – **Adenosine** (Grade D) because of limited procedure-specific and transferable evidence – **Intercostal block** (Grade D) because of insufficient procedure-specific evidence – **High concentrations of oxygen** (Grade B) due to negative procedure-specific evidence – **Electro-acupoint stimulation** (Grade D) due to limited procedure-specific and transferable evidence	– **Corticosteroids for analgesia** (Grade D) due to insufficient procedure-specific evidence – **Adenosine** (Grade D) because of limited procedure-specific and transferable evidence – **Intercostal block** (Grade D) because of insufficient procedure-specific evidence – **High concentrations of oxygen** (Grade B) due to negative procedure-specific evidence – **Electro-acupoint stimulation** (Grade D) due to limited procedure-specific and transferable evidence
Postoperative **not recommended**	– **Mexiletine** (Grade D) because of limited and conflicting procedure-specific evidence – **Paracetamol alone for high intensity pain** (Grade B) due to insufficient analgesic efficacy – **Strong opioids for low-moderate pain** (Grade B) because of a risk of emetic and other side-effects – **IM administration of strong opioids** (Grade B) because of transferable evidence showing unfavourable pharmacokinetics, injection-associated pain, and patient dissatisfaction – **Antibiotics for analgesia (**Grade D) due to limited procedure-specific evidence showing inconsistent results – **Continuous paravertebral block** (Grade D) due to limited procedure-specific evidence – **Thoracic epidural analgesia** (Grade D) due to the risk of complications – **Topical administration of local anaesthetics** (Grade D) due to inconsistent procedure-specific evidence	– **Gabapentinoids** (Grade B) because pain intensity is commonly not severe enough to justify an adjuvant to the usual analgesic agents – **Mexiletine** (Grade D) because of limited and conflicting procedure-specific evidence – **Paracetamol alone for high intensity pain** (Grade B) due to insufficient analgesic efficacy – **Strong opioids for low-moderate pain** (Grade B) because of a risk of emetic and other side-effects – **IM administration of strong opioids** (Grade B) because of transferable evidence showing unfavourable pharmacokinetics, injection-associated pain, and patient dissatisfaction – **Antibiotics for analgesia (**Grade D) due to limited procedure-specific evidence showing inconsistent results – **Continuous paravertebral block** (Grade D) because of the risk of complications – **Thoracic epidural analgesia** (Grade D) due to the risk of complications – **Topical administration of local anaesthetics** (Grade D) due to inconsistent procedure-specific data

	– **Wound application of conventional NSAID via drain** (Grade B) because of procedure-specific and transferable evidence showing a lack of analgesic benefit – **High concentrations of oxygen** (Grade B) due to negative procedure-specific evidence	– **Wound application of conventional NSAID via drain** (Grade B) because of procedure-specific and transferable evidence showing a lack of analgesic benefit – **High concentrations of oxygen** (Grade B) due to negative procedure-specific evidence

*Appendix B: Descriptions of major, minor, and cosmetic breast surgery

Overall PROSPECT Recommendations for Non-Cosmetic Breast Surgery



Evidence review process

Literature search

Systematic review of the literature from 1966–May 2006 using MEDLINE and EmBASE, following the protocol of the Cochrane Collaboration (Appendix C: Breast Surgery: Search terms)

- Inclusion of randomised studies in English, assessing analgesic interventions in breast cancer surgery in adults, and reporting pain on a linear analogue, verbal or numerical rating scale
  - Primary outcome measure: postoperative pain scores
  - Secondary outcome measure: supplemental analgesic requirements, other recovery outcomes (adverse effects, functional recovery)
- Identification of 99 studies of peri-operative interventions for postoperative pain following breast surgery
- 42 studies included (Appendix D: Breast Surgery: Included References)
- 57 studies excluded (Appendix E: Breast Surgery: Excluded references)
- The most common reasons for exclusion were that pain scores were not reported (29 studies), or the study combined data from mixed surgery groups (10 studies) without an identifiable breast surgery subgroup, or the type of surgery was inappropriate (8 studies).

Appendix

A. Levels of evidence and grades of recommendation

From 2006 onwards, the **prospect** methodology has been refined to take more account of the quality of the evidence on which the recommendations are based. The way in which the quality of studies determines the level of evidence, and thereby determines the grade of recommendation, is summarised below. Development of the **prospect** methodology has been an ongoing process, and previous experience indicated the need for these changes, to help clarify the basis for the recommendations.

Sources of evidence in PROSPECT

The evidence for **prospect** is derived from three separate sources, and this evidence is taken into consideration by the **prospect** Working Group to determine the **prospect** recommendations:

- Procedure-specific evidence derived from the systematic reviews of the literature Transferable evidence from comparable procedures, or from other relevant sources, identified by the members of the **prospect** Working Group
- Current practice – a commentary on the interventions from the members of the **prospect** Working Group
- Practical **prospect** recommendations are based on all the information **Study quality assessment**

All cited studies are assessed for quality of reporting of methodology and results (assessment performed by the medical writing team and the **prospect** Subgroup):

1. Statistical analyses and patient follow-up assessment: indicates whether statistical analyses were reported, and whether patient follow-up was greater or lesser than 80%.

2. Allocation concealment assessment: indicates whether there was adequate prevention of foreknowledge of treatment assignment by those involved in recruitment (A adequate, B unclear, C inadequate, D not used). Empirical research has shown that trials with inadequate or unclear allocation concealment report significantly greater estimates of treatment effect than those trials in which concealment was adequate (Chalmers 1983, Schulz 1995, Moher 1998). Allocation concealment was found to be more important for preventing bias than other aspects of study quality, such as generation of the allocation sequence and double-blinding (Chalmers 1983, Schulz 1995, Moher 1998, Higgins JPT, Green S, editors, 2005; http://www.cochrane.org/resources/handbook/hbook.htm (accessed 31st May 2005): Section 6.3.)

3. Numerical scores (total 1–5) for study quality: assigned using the method proposed by Jadad et al 1996, to indicate whether a study reports appropriate randomisation, double-blinding and statements of possible withdrawals. Empirical research found that low-quality trials were associated with an increased estimate of treatment benefit than high-quality trials (Moher 1998)

4. Additional study quality assessment: including an assessment of how closely the study report meets the requirements of the CONSORT statement (Moher 2005) (additional assessment performed by the **prospect** Subgroup)

Grading of recommendations based on overall level of evidence

The recommendations are graded according to the overall level of evidence, which is determined by the quality of studies cited, the consistency of evidence and the source of evidence (as indicated in the table below).

Relationship between quality and source of evidence, levels of evidence and grades of recommendation in PROSPECT

	Study quality assessments					Level of Evidence (LoE)	Grade of recommendation (based on overall LoE, considering balance of clinical practice information and evidence)	
Study type	**Statistical analyses and patient follow-up assessment**		**Allocation concealment**	**Jadad scores**	**Additional assessment of overall study quality required to judge LoE**		**Procedure-specific**	**Transferable**
Systematic review with homogeneous results	N/A		N/A	N/A	N/A	1	A	B
Randomised controlled trial (RCT)	Statistics reported and >80% follow-up	AND	A	(1-5)	N/A	1	A (based on two or more studies or a single large, well-designed study)	B
			OR					
			B	(3-5)	N/A			
			OR					
			B	**(1-2)**	**Yes**			
RCT	Statistics not reported or questionable or <80% follow-up	AND/ OR	**B**	**(1-2)**	**Yes**	2	B (or extrapolation from one procedure-specific LoE 1 study)	C
			OR					
			C	(1-5)	N/A			
			OR					
			D	(1-5)	N/A			
Non-systematic review, cohort study, case study; **(e.g. some adverse effects evidence)**	N/A		N/A			3	C	
Clinical practice information (expert opinion); inconsistent evidence	N/A		N/A			4	D	

B. Descriptions of major, minor, and cosmetic breast surgery

Studies included in the procedure-specific review were of major or minor breast surgery, as described below. Studies of cosmetic surgery were excluded.

Major breast surgery

- Mastectomy:
    - Total or simple - the whole breast, including the nipple and areola, is removed, but not the axillary lymph nodes
    - Partial or segmental - removal of a portion of the breast tissue and a surrounding area of normal breast tissue (usually removes less tissue than a quandrantectomy but more than a lumpectomy or wide excision)
    - Radical - removal of the breast tissue, skin, nipple, areola, underlying chest wall muscles (pectorals) and varying numbers of axillary lymph nodes
    - Modified radical – removal of the whole breast, nipple/areolar region, and most of the axillary lymph nodes, but not the chest wall muscles
    - Unilateral – on one side only
- Quadrantectomy - removes a quarter of the breast, with or without the skin and breast fascia
- Axillary lymph node dissection (or resection or clearance), or axillary lymphadenectomy – surgical removal of the axillary lymph nodes
- Breast reconstruction:
    - transverse rectus abdominis musculocutaneous (TRAM) flap breast reconstruction - uses muscle, skin, and fat from the patient's abdominal wall to reconstruct the breast
    - latissimus dorsi breast reconstruction - uses skin and muscle from the patient's back

Minor breast surgery

- Lumpectomy, breast lump excision, breast biopsy, breast-conserving therapy, wide local excision, breast tumour resection or breast surgery resection - removal of the breast cancer tumor and a surrounding area of normal breast tissue
- Radioisotope-guided (sentinel) lymph node biopsy or sentinel node procedure – involves the removal of only 1–3 sentinel lymph nodes (the first nodes in the lymphatic chain). A radioactive tracer and/or blue dye is injected into an area of the tumor and is taken up by the sentinel nodes, thus enabling the surgeon to identify the lymph node most likely to be cancerous if the disease has spread from its original source

Cosmetic breast surgery

- Reduction mammoplasty – breast reduction surgery

- Breast augmentation - breast enlargement operation that usually involves placing an artificial implant either under the breast tissue, or under the chest muscle behind the breast.

C. Breast Surgery: Search terms

(pain OR analgesi* OR anaesthe* OR anesthe* OR vas OR "visual analog*" OR vrs OR mcgill OR epidural OR neuraxial OR intrathecal OR spinal OR caudal OR "peripheral nerve" OR "peripheral block" OR "regional nerve" OR “paravertebral block” OR “intercostal nerve” OR infiltration OR instillation OR NSAID OR COX-2 OR paracetamol OR acetaminophen OR gabapentin OR pregabalin OR clonidine OR opioid OR ketamine OR corticosteroid OR “patient controlled analgesia” OR PCA) AND ("radical mastectomy" OR mastectomy OR mammectomy OR lumpectomy or “axillary node dissection” OR “axillary node clearance” OR “wedge resection” OR “skin-sparing mastectomy” OR “breast reconstruction” OR “lattissimus dorsi flap” OR “TRAM flap” OR “implant reconstruction” OR “breast surgery”)

D. Breast Surgery: Included References

1. Abou Zeid H, Al GA, Abdul HM. Dolasetron decreases postoperative nausea and vomiting after breast surgery. Breast Journal 2002; 8(4):216-221.
2. Adam F, Libier M, Oszustowicz T, Lefebvre D, Beal J, Meynadier J. Preoperative small-dose ketamine has no preemptive analgesic effect in patients undergoing total mastectomy. Anesthesia and Analgesia 1999; 89(2):444-7.
3. Aida S, Baba H, Yamakura T, Taga K, Fukuda S, Shimoji K. The effectiveness of preemptive analgesia varies according to the type of surgery: a randomized, double-blind study. Anesthesia and Analgesia 1999; 89(3):711-6.
4. Ansanelli VW, Lesser ML. A prospective, randomized trial of the use of CO2 laser vs. scalpel in breast cancer surgery. Breast Disease 1996; 9(3):125-130.
5. Atanassoff PG, Alon E, Weiss BM. Intercostal nerve block for lumpectomy: superior postoperative pain relief with bupivacaine. Journal of Clinical Anesthesia 1994; 6(1):47-51.
6. Bosek V, Cox CE. Comparison of analgesic effect of locally and systemically administered ketorolac in mastectomy patients. Annals of Surgical Oncology: the official journal of the Society of Surgical Oncology 1996; 3(1):62-6.
7. Buggy DJ, Kerin MJ. Paravertebral analgesia with levobupivacaine increases postoperative flap tissue oxygen tension after immediate latissimus dorsi breast reconstruction compared with intravenous opioid analgesia. Anesthesiology 2004; 100(2):375-80.
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15. Fassoulaki A, Sarantopoulos C, Melemeni A, Hogan Q. Regional block and mexiletine: the effect on pain after cancer breast surgery. Regional Anesthesia and Pain Medicine 2001; 26(3):223-8.
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17. Gan TJ, Jiao KR, Zenn M, Georgiade G. A randomized controlled comparison of electro-acupoint stimulation or ondansetron *versus* placebo for the prevention of postoperative nausea and vomiting. Anesthesia and Analgesia 2004; 99(4):1070-5.
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E. Breast Surgery: Excluded references

Reference details	**Reason for exclusion**
Abdul LMS, Putland AJ, McCluskey A, Meadows DP, Remington SA. Oral midazolam premedication for day case breast surgery, a randomised prospective double-blind placebo-controlled study. Anaesthesia 2001; 56(10):990-4.	no pain scores
Abdullah TI, Iddon J, Barr L, Baildam AD, Bundred NJ. Prospective randomized controlled trial of preservation of the intercostobrachial nerve during axillary node clearance for breast cancer. British Journal of Surgery 1998; 85(10):1443-1445.	no pain scores
Anand R, Skinner R, Dennison G, Pain JA. A prospective randomised trial of two treatments for wound seroma after breast surgery. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2002; 28(6):620-2.	no pain scores
Atanassoff PG, Alon E, Pasch T, Ziegler WH, Gautschi K. Intercostal nerve block for minor breast surgery. Regional Anesthesia 1991; 16(1):23-7.	no pain scores
Bonezzi C, Miotti D, Bettaglio R, Demartini L, Stephen R. Electromotive drug administration (EMDA) for pain following mastectomy. European Journal of Pain 1993; 14(3):65-66.	case study
Bosek V, Smith DB, Cox C. Ketorolac or fentanyl to supplement local anesthesia? Journal of Clinical Anesthesia 1992; 4(6):480-3.	Surgery included lumpectomy, biopsy or central venous catheter placement, not separated
Brozovic G, Vrdoljak DV, Ramljak V. Analgesia after surgery for breast tumor. Libri Oncologici 2003; 31(1-3):75-79.	review paper
Bundred N, Maguire P, Reynolds J, Grimshaw J, Morris J, Thomson L, Barr L, Baildam A. Randomised controlled trial of effects of early discharge after surgery for breast cancer. British Medical Journal (Clinical research ed.) 1998; 317(7168):1275-9.	no pain scores
Chadbourne EB, Zhang S, Gordon MJ, Ro EY, Ross SD, Schnur PL, Schneider RPR. Clinical outcomes in reduction mammaplasty: A	review paper

systematic review and meta-analysis of published studies. Mayo Clinic Proceedings 2001; 76(5):503-510.	
Chan, M.T., et al., Single-dose tropisetron for preventing postoperative nausea and vomiting after breast surgery. Anesthesia and analgesia, 1998. 87(4): p. 931-5.	anti-emetics study
Chiu CL, Chan YK, Ong GS, Delilkan AE. A comparison of the maintenance and recovery charcateristic of sevoflurane-nitrous oxide against isoflurane-nitrous oxide anaesthesia. Singapore Medical Journal 2000; 41(11):530-3.	no pain scores
Daltrey I, Thomson H, Hussien M, Krishna K, Rayter Z, Winters ZE. Randomized clinical trial of the effect of quilting latissimus dorsi flap donor site on seroma formation. The British Journal of Surgery 2006; 93(7):825-30.	breast reconstruction
Doss NW, Ipe J, Crimi T, Rajpal S, Cohen S, Fogler RJ, Michael R, Gintautas J. Continuous thoracic epidural anesthesia with 02% ropivacaine *versus* general anesthesia for perioperative management of modified radical mastectomy. Anesthesia and analgesia 2001; 92(6):1552-7.	inappropriate randomisation
Dua N, Bhatnagar S, Mishra S, Singhal AK. Granisetron and ondansetron for prevention of nausea and vomiting in patients undergoing modified radical mastectomy. Anaesthesia and Intensive Care 2004; 32(6):761-4.	no pain scores
Eija K, Tiina T, Pertti N. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain 1995; 64:293-302	10 week study of patients with neuropathic pain following breast surgery
Eldrup J, Wied U, Andersen B. Randomised trial comparing Proximate stapler with conventional skin closure. Acta Chirurgica Scandinavica 1981; 147(7):501-2.	mixed surgery, abdominal and breast, not separated
Enqvist B, Björklund C, Engman M, Jakobsson J. Preoperative hypnosis reduces postoperative vomiting after surgery of the breasts A prospective, randomized and blinded study. Acta Anaesthesiologica Scandinavica 1997; 41(8):1028-32.	emesis study using hypnosis
Fassoulaki A. Brachial plexus block for pain relief after modified radical mastectomy. Anesthesia and Analgesia 1982; 61(12):986-7.	no pain scores
Fassoulaki A, Sarantopoulos C, Derveniotis C. Physostigmine increases the dose of propofol required to induce anaesthesia. Canadian Journal of Anaesthesia = Journal canadien d'anesthésie 1997; 44(11):1148-51.	no pain scores
Fayman M, Beeton A, Potgieter E, Becker PJ. Comparative analysis of bupivacaine and ropivacaine for infiltration analgesia for bilateral breast surgery. Aesthetic Plastic Surgery 2003; 27(2):100-3.	cosmetic breast surgery, either augmentation or reduction

Gan, T.J., et al., Double-blind, randomized comparison of ondansetron and intraoperative propofol to prevent postoperative nausea and vomiting. Anesthesiology, 1996. 85(5): p. 1036-42.	anti-emetics study
Gerber L, Lampert M, Wood C, Duncan M, D'Angelo T, Schain W, McDonald H, Danforth D, Findlay P, Glatstein E, et al. Comparison of pain, motion, and edema after modified radical mastectomy vs local excision with axillary dissection and radiation. Breast Cancer Research and Treatment 1992; 21(2):139-45.	no pain scores
Groeben H, Schäfer B, Pavlakovic G, Silvanus MT, Peters J. Lung function under high thoracic segmental epidural anesthesia with ropivacaine or bupivacaine in patients with severe obstructive pulmonary disease undergoing breast surgery. Anesthesiology 2002; 96(3):536-41.	no pain scores
Guo X, Yi J, Ye T, Luo A, Huang Y, Ren H. Comparison of remifentanil and fentanyl in patients undergoing modified radical mastectomy or total hysterectomy. Chinese Medical Journal 2003; 116(9):1386-90.	mixed surgery: radical mastectomy and total hysterectomy; no pain scores
Hammas B, Thörn SE, Wattwil M. Superior prolonged antiemetic prophylaxis with a four-drug multimodal regimen - comparison with propofol or placebo. Acta Anaesthesiologica Scandinavica 2002; 46(3):232-7.	anti-emetics study
Hegi TR, Bombeli T, Seifert B, Baumann PC, Haller U, Zalunardo MP, Pasch T, Spahn DR. Effect of rofecoxib on platelet aggregation and blood loss in gynaecological and breast cancer surgery compared with diclofenac. British Journal of Anaesthesia 2004; 92(4):523-531.	mixed surgery: hysterectomy and breast
Heitz L, Symreng T, Scamman FL. Effect of music therapy in the postanesthesia care unit: a nursing intervention. Journal of Post Anesthesia Nursing 1992; 7(1):22-31.	mixed surgery: thyroid, parathyroid and breast
Hussain SM. Failure of diclofenac sodium suppository to augment nalbuphine hydro- chloride post-operative analgesia after daycare surgery. Specialist 1998; 14(3):267-270.	no randomisation
Imai Y, Mammoto T, Murakami K, Kita T, Sakai T, Kagawa K, Kirita T, Sugimura M, Kishi Y. The effects of preanesthetic oral clonidine on total requirement of propofol for general anesthesia. Journal of Clinical Anesthesia 1998; 10(8):660-5.	no pain scores
Johansen J, Overgaard J, Blichert TM, Overgaard M. Treatment morbidity associated with the management of the axilla in breast-conserving therapy. Acta Oncologica 2000; 39(3):349-354.	breast conserving therapy; no pain scores
Kakagia D, Fotiadis S, Tripsiannis G. Levobupivacaine *versus* ropivacaine infiltration analgesia for mastopexy: A comparative study of 2 long-acting anesthetic drugs in infiltrative anesthesia for mastopexy. Annals of Plastic Surgery 2005; 55(3):258-261.	mastopexy (breast lift); no randomisation

Kakehata J, Ogino H, Sasaki K, Mashio H, Gohda Y, Komura Y, Imai M, Kemmotsu O. Postoperative pain relief by preanesthetic administration of buprenorphine suppository in elective mastectomy. Japanese Journal of Anesthesiology 1993; 42(8):1184-1189.	Japanese; randomised?
Kasaba T, Yoshikawa G, Seguchi T, Takasaki M. Epidural fentanyl improves the onset and spread of epidural mepivacaine analgesia. Canadian Journal of Anaesthesia 1996; 43(12):1211-1215.	no pain scores
Klein SM, Bergh A, Steele SM, Georgiade GS, Greengrass RA. Thoracic paravertebral block for breast surgery. Anesthesia and Analgesia 2000; 90(6):1402-5.	cosmetic breast surgery, augmentation or reconstruction
Laisalmi M, Eriksson H, Koivusalo AM, Pere P, Rosenberg P, Lindgren L. Ketorolac is not nephrotoxic in connection with sevoflurane anesthesia in patients undergoing breast surgery. Anesthesia and Analgesia 2001; 92(4):1058-63.	no pain scores
Laisalmi M, Teppo AM, Koivusalo AM, Honkanen E, Valta P, Lindgren L. The effect of ketorolac and sevoflurane anesthesia on renal glomerular and tubular function. Anesthesia and Analgesia 2001; 93(5):1210-3.	no pain scores
Layeeque R, Hochberg J, Siegel E, Kunkel K, Kepple J, Henry TRS, Dunlap M, Seibert J, Klimberg VS. Botulinum toxin infiltration for pain control after mastectomy and expander reconstruction. Annals of Surgery 2004; 240(4):608-13.	not randomised; mastectomy with tissue expander placement; no pain scores
Legeby M, Segerdahl M, Sandelin K, Wickman M, Ostman K, Olofsson C. Immediate reconstruction in breast cancer surgery requires intensive post-operative pain treatment but the effects of axillary dissection may be more predictive of chronic pain. Breast (Edinburgh Scotland) 2002; 11(2):156-62.	randomisation by date of birth
Lindahl JB, Nydert P, Giesecke K, Persson PM, Movin T, Segerdahl M. Pre-packed take-home analgesics in ambulatory surgery. Acute Pain 2006; 8(1):13-21.	mixed surgeries: 'breast surgery' (not defined), knee arthroscopy, varicose veins or anal fistulae
Lotze MT, Duncan MA, Gerber LH, et a. Early *versus* delayed shoulder motion following axillary dissection. A randomized prospective study. Annals of Surgery 1981; 193(3):288-295.	no pain scores
McCarthy PM, Martin JK, Jr., Wells DC, Welch JS, Ilstrup DM. An aborted, prospective, randomized trial of sclerotherapy for prolonged drainage after mastectomy. Surgery Gynecology & Obstetrics 1986; 162(5):418-20.	no pain scores; study aborted early due to severe pain associated with sclerosing treatment
Morley FP, Newton PT, Cook MJ. Ketorolac and indomethacin are equally efficacious for the relief of minor postoperative pain. Canadian Journal of Anaesthesia = Journal Canadien d'anesthésie 1993; 40(12):1126-30.	mixed surgeries: breast biopsy, diagnostic laparoscopy or cervical conization

Paredes JP, Puente JL, Potel J. Variations in sensitivity after sectioning the intercostobrachial nerve. American Journal of Surgery 1990; 160(5):525-8.	prospective study; no randomisation; no treatment groups; no pain scores
Purhonen S, Niskanen M, Wüstefeld M, Mustonen P, Hynynen M. Supplemental oxygen for prevention of nausea and vomiting after breast surgery. British Journal of Anaesthesia 2003; 91(2):284-7.	absence of pain-related information
Purushotham AD, McLatchie E, Young D, George WD, Stallard S, Doughty J, Brown DC, Farish C, Walker A, Millar K, Murray G. Randomized clinical trial of no wound drains and early discharge in the treatment of women with breast cancer. The British Journal of Surgery 2002; 89(3):286-92.	no pain scores
Reihnér E, Grunditz R, Giesecke K, Gustafsson LL. Postoperative nausea and vomiting after breast surgery: efficacy of prophylactic ondansetron and droperidol in a randomized placebo- controlled study. European Journal of Anaesthesiology 2000; 17(3):197-203.	no pain scores
Riest G, Peters J, Weiss M, Pospiech J, Hoffmann O, Neuhäuser M, Beiderlinden M, Eikermann M. Does perioperative administration of rofecoxib improve analgesia after spine, breast and orthopaedic surgery? European Journal of Anaesthesiology 2006; 23(3):219-226.	mixed surgeries: spine, breast and orthopaedic
Rosaeg O, Bell M, Cicutti N, Dennehy K, Lui A, Krepski B. Pre-incision infiltration with lidocaine reduces pain and opioid consumption after reduction mammoplasty. Regional Anesthesia and Pain Medicine 1999; 23(6):575-9.	reduction mammoplasty for mammary hypertrophy
Salmon RJ, Ansquer Y, Asselain B. Preservation *versus* section of intercostal-brachial nerve IBN in axillary dissection for breast cancer--a prospective randomized trial. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 1998; 24(3):158-61.	no pain scores
Shamley DR, Barker K, Simonite V, Beardshaw A. Delayed *versus* immediate exercises following surgery for breast cancer: a systematic review. Breast Cancer Research and Treatment 2005; 90(3):263-71.	review paper; no pain scores
Sperhacke D, Geier KO, Eschiletti JCC. High thoracic epidural anesthesia associated or not to low thoracic epidural anesthesia in outpatient procedures: Clinical implications. Revista Brasileira de Anestesiologia 2004; 54(4):479-490.	cosmetic breast surgery; no pain scores
Strømskag KE, Hauge O, Steen PA. Distribution of local anesthetics injected into the interpleural space, studied by computerized tomography. Acta Anaesthesiologica Scandinavica 1990; 34(4):323-6.	mixed surgeries: cholecystectomy, renal or breast surgery
Tang J, White PF, Wender RH, Naruse R, Kariger R, Sloninsky A, Karlan MS, Uyeda RY, Karlan SR, Reichman C, Whetstone B. Fast-track office-based anesthesia: A comparison of propofol *versus* desflurane with	mixed surgeries: hernia repair, partial mastectomy and 'others'; no pain scores

antiemetic prophylaxis in spontaneously breathing patients. Anesthesia and Analgesia 2001 Jan; 92(1):95-9.	
Vanacker BF. The impact of nitrous oxide on postoperative nausea and vomiting after desflurane anesthesia for breast surgery. Acta Anaesthesiologica Belgica 1999; 50(2):77-81.	'breast surgery' not defined; no pain scores
Watson CP, Evans RJ. The postmastectomy pain syndrome and topical capsaicin: a randomized trial. Pain 1992; 51(3):375-9.	not surgical study; treatment of postmastectomy pain syndrome
Wattwil M, Thörn SE, Lövqvist A, Wattwil L, Gupta A, Liljegren G. Dexamethasone is as effective as ondansetron for the prevention of postoperative nausea and vomiting following breast surgery. Acta Anaesthesiologica Scandinavica 2003; 47(7):823-7.	anti-emetics study
Whelan TJ, Levine M, Julian J, Kirkbride P, Skingley P. The effects of radiation therapy on quality of life of women with breast carcinoma: Results of a randomized trial. Cancer 2000; 88(10):2260-2266.	no pain scores