

The Great Anesthetic Debate: Cons of TIVA

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Why Does This Matter?

- Propofol was discovered in 1973 by veterinarian, John Glen and three anesthesiologists at Imperial Chemical Industries (now AstraZeneca)
- Approved in the UK in 1986, FDA approved in the US in 1989
- Important to reassess our current practices
 - Propofol has replaced Thiopental
 - Propofol has not replaced volatile anesthetics

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Outline

- Short & long-term outcomes
 - Propofol based TIVAs vs No difference vs Conflicting
- Clear advantages of TIVA
- Disadvantages of TIVA

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Outcomes

- Short:
 - PONV
 - Emergence
 - Post-operative pain
 - PACU stay
 - Delirium & emergence time from anesthesia
 - Ischemia reperfusion injury
 - Major Adverse Cardiac Events (MACE)

- Long term:
 - Survival
 - Post-operative persistent pain
 - Recurrence of malignancy
 - Rejection

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Post-operative Nausea and Vomiting - Propofol




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Emergence - Conflicting


- Overall, a paucity of strong literature on emergence
- Randomized Clinical Trial: 2019, (Jo et al.) looked at the effect of TIVA vs Volatiles on emergence agitation after nasal surgery in 80 patients:
 - Richmond Agitation–Sedation Scale (RASS) and the Riker Sedation–Agitation Scale (RSAS)
 - RASS score of 1: 2.5% incidence in the TIVA group vs 20% incidence in the Volatile group, risk difference of 17.5 (95% CI, 3.6–31.4)
 - RSAS score of 5: 2.5% incidence in the TIVA group vs 25% incidence in the Volatile group, risk difference of 22.5 (95% CI, 7.3–37.7)
- Large Meta-analysis: 2018, (Schraag et al.) 21,000 patients undergoing GA for a wide range of surgical cases:
 - No significant difference in emergence agitation
 - Faster respiratory recovery and time to tracheal extubation in the volatile anesthetic group compared to TIVA

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PACU Stay – Conflicting

- Schraag, et al meta-analysis found
 - PACU time was shorter with TIVA
 - Time to respiratory recovery was shorter with sevoflurane
 - No difference in psychomotor recovery



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PACU Stay – Conflicting

- Chan et al's, retrospective single center study looked at 395 patients undergoing colorectal surgery who received either desflurane or TIVA
 - No difference in PACU time

	Group DES (n = 219)	Group TIVA (n = 176)	P value
Waiting for anesthesia time (min)	7.8 ± 3.5	7.7 ± 3.7	0.81
Surgical time (min)	178.7 ± 45.7	180.1 ± 42.7	0.77
Anesthesia time (min)	214.6 ± 46.7	214.1 ± 45.1	0.90
Extubation time (min)	9.8 ± 4.4	9.5 ± 3.8	0.39
Exit from operating room after extubation (min)	9.4 ± 2.7	9.2 ± 2.7	0.63
Total operating room time (min)	231.8 ± 47.0	230.8 ± 46.1	0.84
PACU time (min)	49.8 ± 12.3	49.9 ± 11.7	0.94

DES, desflurane anesthesia; TIVA, total intravenous anesthesia; PACU, post-anesthesia care unit.
Data are shown as mean ± SD or number.
doi:10.1371/journal.pone.0165407.t003

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Comparison Of The Amount Of Anesthetic Drugs Used Surgical Between Desflurane And TIVA Groups

	Group DES (n = 219)	Group TIVA (n = 176)	P value
Fentanyl (µg/kg)	2.9 ± 0.7	4.5 ± 1.0	<0.001
Cisatracurium (mg/kg)	0.2 ± 0.1	0.3 ± 0.1	<0.001
Neostigmine (µg/kg)	32.2 ± 4.4	33.0 ± 4.4	0.08
Glycopyrrolate (µg/kg)	6.4 ± 0.9	6.5 ± 0.9	0.08

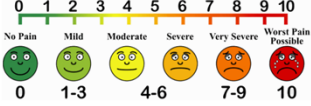
DES, desflurane anesthesia; TIVA, total intravenous anesthesia.
Data are shown as mean ± SD or number.
doi:10.1371/journal.pone.0165407.t002

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Post-operative Pain - Conflicting

- Conflicting evidence on post-operative pain – may depend on the procedure
 - Hepatobiliary surgery – more evidence that TIVAs reduce postoperative pain
 - Spine surgery - more evidence that TIVAs reduce postoperative pain
 - Thyroid surgery – more evidence that VAs reduce postoperative pain
 - Bariatric surgery – no difference
 - Cardiac surgery – no difference




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Delirium - Conflicting

- Neuraxial anesthesia is an independent protective factor
- Mei et al, looked at 209 elderly patients receiving total hip and knee replacements
 - 9.7% increased chance of postoperative delirium in TIVA compared to sevoflurane at days 1, 2, and 3
 - Issues with power
- Miller et al meta-analysis compared maintenance of GA for 4500 elderly people undergoing non-cardiac surgery using propofol-based TIVA vs Volatiles
 - No difference in incidence of delirium
- Zhang et al, RCT of 387 elderly patients having cancer surgery with TIVA vs Sevoflurane
 - Propofol group had a lower incidence of postop cognitive decline measured at 7 days after the surgery



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Ischemia Reperfusion Injury In Liver Transplantation - No Difference

- Sevoflurane conditioning has been identified to provide protection against myocardial ischemia reperfusion injury in animal experiments
- Propofol is thought to have some neuroprotective effects against cerebral ischemia-reperfusion injury
- A recent multicenter, randomized controlled trial that compared propofol with sevoflurane in liver transplantation; showed no difference in biochemical markers of acute organ injury and clinical outcomes between the 2 regimens¹

1. Beck-Schimmer, Beatrice; Bonvini, John M, et al. Conditioning With Sevoflurane in Liver Transplantation. Transplantation: August 2015 - Volume 99 - Issue 8 - p 1605-1612

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Major Adverse Cardiac Events – No Difference

- Yoon et al, looked at risk of major adverse cardiovascular and cerebral events (MACCE) in patients who underwent non-cardiac surgery within 5 years post-coronary stenting: TIVA vs sevoflurane vs desflurane
 - No difference in the incidence of MACCE between the different groups
- Per ACC/AHA guidelines: Either volatile anesthetic agents or TIVA is reasonable for patients undergoing noncardiac surgery, and the choice is determined by factors other than the prevention of myocardial ischemia and myocardial infarction

Yoon HK, An K, Park SK, Ji SH, Jang YE, Yoo S, Kim JT, Kim WH. Anesthetic Agents and Cardiovascular Outcomes of Noncardiac Surgery after Coronary Stent Insertion. J Clin Med. 2020 Feb 5;9(2):428.

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Patient Survival - Conflicting

- Schraag et al meta-analysis from 2018, found no difference in hospital mortality between TIVA and volatile groups in patients receiving ambulatory and inpatient general surgeries (not limited to cancer)
- Hong et al, found no differences in 5-year overall survival between TIVA and volatile anesthetic groups in patients who underwent major cancer surgeries
- Wigmore et al, found a hazard ratio (HR) of 1.46 with the use of volatiles over TIVA at a comprehensive cancer center
 - Study had significant flaws including:
 - No staging data for cancer
 - With propensity matching, the HR was only significant for patients with gastrointestinal tumors
- Need more RCTs (many are underway)

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PERIOPERATIVE MEDICINE

ANESTHESIOLOGY

Volatile versus Propofol General Anesthesia and Long-term Survival after Breast Cancer Surgery: A National Registry Retrospective Cohort Study

Wang L, et al. Anesthesiology. 2022;137(3):315-326.

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Volatile general anesthesia and propofol general anesthesia are commonly used for breast cancer surgery.
- Propofol general anesthesia is associated with lower rates of postoperative nausea and vomiting, but higher rates of hypotension and respiratory depression.
- Propofol general anesthesia is associated with lower rates of postoperative delirium and cognitive dysfunction.
- Propofol general anesthesia is associated with lower rates of postoperative pain.
- Propofol general anesthesia is associated with lower rates of postoperative bleeding.
- Propofol general anesthesia is associated with lower rates of postoperative infection.
- Propofol general anesthesia is associated with lower rates of postoperative mortality.

What This Article Adds to This Topic

- This study found that patients who received volatile general anesthesia had significantly higher rates of long-term survival compared with patients who received propofol general anesthesia.
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Overall survival by type of anesthesia in the unmatched cohort, in which 4,801 subjects received inhaled volatiles and 13,873 subjects received propofol, respectively.

Follow up time, in years	Inhaled volatiles	Propofol
0	4801	13873
1	4011	11919
2	3240	10217
3	2533	8422
4	1911	7029
5	1494	5881
6	1198	4888

From: Volatile versus Propofol General Anesthesia and Long-term Survival after Breast Cancer Surgery: A National Registry Retrospective Cohort Study. Anesthesiology. 2022;137(3):315-326.

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Overall survival by type of anesthesia for 4,658 pairs from a full propensity score match of patients given an inhaled volatile anesthetic or propofol for anesthesia maintenance for breast cancer surgery.

Follow up time, in years	Inhaled volatiles	Propofol
0	4658	4658
1	4053	4058
2	3111	3058
3	2154	2085
4	1165	1085
5	688	617
6	198	214

From: Volatile versus Propofol General Anesthesia and Long-term Survival after Breast Cancer Surgery: A National Registry Retrospective Cohort Study. Anesthesiology. 2022;137(3):315-326. doi:10.1097/ALN.0000000000000309

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Recurrence of Malignancy - Conflicting

- Laboratory studies have suggested that volatile agents are pro-inflammatory, suppress immune cell function and tumor cell killing
- Oh et al's 2018 study showed no difference in recurrence of nonsmall cell lung cancer between the two groups
- Zhang et al's RCT showed propofol decreased local recurrence of breast cancer for patients undergoing primary resection with the goal of breast conservation¹.
 - 2036 women of Asian descent randomized to receive either propofol TIVA and PVB vs volatile anesthesia and PVB.
 - Women who received propofol showed a significant reduction in local recurrence risk; however, there was no difference in risk of metastatic conversion
- More data is needed

1. Zhang L, Chang C-L, Lu C-C, Chen H-M, Wu S-Y. Paracetamol Block in Regional Anesthesia with Propofol Sedation Reduces Locoregional Recurrence in Patients with Breast Cancer Receiving Breast Conservative Surgery Compared with Volatile Inhalational without Propofol in General Anesthesia. Breast Pharmacother (2023) 1:23-31(2023).

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Ongoing Clinical Research Trials In Cancer Surgery

Trial identifier	Cancer type	Study type	Estimated enrollment number	Study arms	Estimated completion date	Primary outcome	Secondary outcomes
NCT01786329	Colorectal cancer	Randomized, quadruple masking	450	Propofol vs. sevoflurane	Dec 2021. Recruiting	Survival, recurrence	LOS, post op chronic pain
NCT03340096	All cancers	Randomized double blind	2,000	Propofol vs. inhalational	Aug 2023. Recruiting	All-cause mortality	Recurrence free survival
NCT03193710	Colorectal cancer	Case control	260	Propofol vs. sevoflurane	Oct 2023. Recruiting	5-year cancer free survival	Recurrence rate, metastasis rate
NCT01970064	Breast and colorectal cancer	Randomized, single blind	8,000	Propofol vs. sevoflurane	Dec 2023. Recruiting	5-year survival	1-year survival
NCT04140013	Colorectal and non-small cell lung cancer	Randomized, quadruple blinding	5,795	Propofol vs. sevoflurane	May 2025. Not yet recruiting	Disease free survival	Overall survival, days alive and at home, return to intended oncological treatment
NCT04255388	Colon cancer	Randomized double blind	792	Propofol vs. sevoflurane	Feb 2026. Recruiting	5-year survival	1/25-year recurrence free survival, 1/5-year survival

From: Propofol TIVA versus inhalational anesthesia for cancer surgery, Digestive Medicine Research

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Persistent Postoperative Pain – No Difference

- Persistent postoperative pain – pain that lasts more than 2 months post-surgery without other causes of pain
- Strong evidence supports regional anesthesia & intraoperative lidocaine infusions preventing persistent postoperative pain
- 2021 RCT by Yu, et al followed 500 patients after cardiac surgery for 3, 6, and 12 months post-surgery
 - Propofol did not reduce persistent pain after cardiac surgery compared with volatile anesthetics

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Graft Rejection - No Difference

- VAPOR-1 randomized controlled trial: (Nieuwenhuijs-Moeke et al) were unable to find any difference in graft outcomes in patients receiving living donor kidney transplants using propofol vs sevoflurane vs PROSE (Propofol for donor, sevoflurane for recipient)

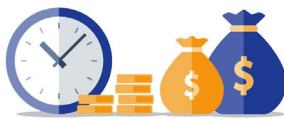
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Cons

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Costs

- Greater direct costs associated with TIVA
 - Higher costs for anesthetics, analgesics, and muscle relaxants with propofol TIVA



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Logistics

- Second IV (or one IV that is visible to the anesthesiologist)
- Alaris pump
- Electroencephalogram (EEG) monitoring
 - Bispectral Index (BIS) monitor: analyzes
 - Entropy monitor: analyzes EEG and frontal electromyograph signals
- Proper training on TIVA and EEG monitoring (BIS and Entropy)

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Risk of Intraoperative Awareness

- Reported incidence of 0.25% up to 1.1% in TIVA cases
- Other factors that further increase the chances of awareness:
 - Patient history of awareness under general anesthesia
 - Obesity
 - Use of neuromuscular blockers
 - Lack of processed electroencephalogram (EEG) monitoring
 - Cardiac, obstetrics, trauma cases




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Hemodynamic instability

- TIVA may be more challenging to titrate in certain conditions
 - Setting of severe blood loss
 - Pheochromocytomas - 7/2022 retrospective study by Kim et al : TIVA was independently associated with intraoperative hemodynamic instability compared to balanced anesthesia with sevoflurane in adrenalectomies for pheochromocytomas



Kim WW, Kim DH, Cho JW, Bah CS, Lee YM, Chung KW, Koh JM, Lee SH, Hong SI, Kim YI, Sung TY. The association between the type of anesthesia and hemodynamic instability during pheochromocytoma surgery: a retrospective cohort study. *Surg Endosc*. 2022 Jul;36(7):1489-1500



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Special Populations



- Chronic pain patients on chronic opioids
- Critically ill patients & risk of propofol related infusion syndrome
- Morbid obesity

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Drug Monitoring


- We can monitor the end-tidal concentration of volatile anesthetics in real time
 - Minimum Alveolar Concentration (MAC)
- We do not have a means of monitoring propofol in the patient's blood stream
 - We only have target controlled infusions which predicts the drug concentration in the central compartment

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Conclusion

- There are many settings where TIVA is most advantageous
 - MH patients, muscular dystrophy
 - PONV
 - Shorter procedures (possibly)
- There is inconsistent literature or no literature behind other purported advantages to TIVA
- TIVA has higher upfront costs
- TIVA requires adequate training and specific logistics
- There may be special populations that make TIVA challenging



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References

- Schraag S, Pradelli L, Alsheli AJ, et al. Propofol vs. inhalational agents to maintain general anaesthesia in ambulatory and in-patient surgery: a systematic review and meta-analysis. *BMC Anaesthesiol* 18, 52 (2018).
- Beck-Schimmer, Beatrice; Bonvini, John M. et al. Conditioning With Sevoflurane in Liver Transplantation, Transplantation: August 2015 - Volume 99 - Issue 8 - p 1506-1512
- Xu Z, Yu J, Wu J, et al. The Effects of Two Anesthetics, Propofol and Sevoflurane, on Liver Ischemia/Reperfusion Injury. *Cell Physiol Biochem* 2016;38:1553-1562.
- Shin, Seokyoung; Ito, Dong J; Kim, Myoung S, et al. Propofol intravenous anaesthesia with dexflurane compared with dexflurane alone on postoperative liver function after living-donor liver transplantation. *European Journal of Anaesthesiology*, September 2019 - Volume 36 - Issue 9 - p 656-666
- Wong, S.S.C., Choi, E.K.Y., Chan, W.S., et al. Propofol total intravenous anaesthesia versus inhalational anaesthesia for acute postoperative pain in patients with morphine patient-controlled analgesia: a large-scale retrospective study with covariate adjustment. *BMC Anaesthesiol* 22, 140 (2022)
- Alkhatib H, Fagardet MW, Gosselin G, et al. Pain and nausea after bariatric surgery with total intravenous anaesthesia versus dexflurane anaesthesia: a double blind, randomized, controlled trial. *Surg Obes Relat Dis*. 2019 Sep;15(9):1505-1512. doi: 10.1016/j.soard.2019.05.020. Epub 2019 May 14.
- Qiu Q, Chai DM, Wong SSC, Irwin MD, Chung CW. Effects of intra-operative maintenance of general anaesthesia with propofol on postoperative pain outcomes - a systematic review and meta-analysis. *Anaesthesia*. 2021;76:1229-33
- Mei X, Zhang HL, Li C, Ma X, Zheng H, Marcantonio E, Xia Z, Shen Y. The Effects of Propofol and Sevoflurane on Postoperative Delirium in Older Patients: A Randomized Clinical Trial Study. *J Alzheimers Dis*. 2020;76(4):1627-1636.
- Zhang Y, Shen GG, Zhang YK, Cao SJ, Zhu SN, Li HL, Ma D, Wang DR and The First Study of Perioperative Organ Protection (SPOP) Investigators (2018) Propofol compared with sevoflurane general anaesthesia is associated with delayed delayed neurocognitive recovery in older adults. *BMJ*. 175, 509-524
- Bassouni AS, Amy YM. Cardioprotective effect of sevoflurane in patients with coronary artery disease undergoing vascular surgery. *Saudi J Anaesth*. 2012 Apr 6(2):125-30
- Hong B, Lee S, Kim Y, Lee M, Youn AM, Kim H, Hong SH, Kim YH, Yoon SH, Lim C. Anesthetics and long-term survival after cancer surgery-total intravenous versus volatile anaesthesia: a retrospective study. *BMC Anaesthesiol*. 2019 Dec;19(1):133
- Wigmore TL, Mohammed K, Rhanj S. Long-term Survival for Patients Undergoing Volatile versus IV Anesthesia for Cancer Surgery: A Retrospective Analysis. *Anesthesiology*. 2016 Jan;124(1):69-79

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References Continued

- Day A, Lopez-Chico MA, Dubois J, Bellar J, Budge A; Global Onco-Anesthesia Research Collaboration Group. Anesthetic technique and cancer outcomes: a meta-analysis of total intravenous versus volatile anesthesia. *Curr Anesth Sedat*. 2018 Mar;20(3):246-262. Epub 2018.
- Ohn T, Kim K, Breen S, Lee J, Do SH, Cheung JM, et al. Long-term oncologic outcomes for patients undergoing volatile versus intravenous anesthesia for non-small cell lung cancer surgery: a retrospective propensity matching analysis. *Cancer Control*. 2018.
- Edwards ZF, Kellner LS. Propofol-TIVA versus Inhalational anesthesia for cancer surgery. *Digestive Medicine Research*. 2020 June; 3(26):21-28; Table 1
- Yu H, Li F, Dai M, Jiang A, He LL, Zhang JQ, Yu H. The Effect of Propofol Versus Volatile Anesthetics on Persistent Pain After Cardiac Surgery: A Randomized Controlled Trial. *J Cardiothorac Vasc Anesth*. 2021 Feb;35(2):238-245.
- Naoumchik M, Mooka G, Nawaamhuk V, Saitan M, et al. Propofol based anaesthesia versus sevoflurane based anaesthesia for living donor kidney transplantation: results of the VAPOR 1 randomized controlled trial. *BMJ Open*. 2019;9(10):e020184.
- Kim W, Kim DH, Chu JY, Park CS, Lee JM, Chung KW, Kim BS, Lee SH, Hong SJ, Kim YJ, Sung TY. The association between the type of anesthesia and hemodynamic instability during pheochromocytoma surgery: a retrospective cohort study. *Yonsei Medical Journal*. 2022 Apr; 63(4):461-469.
- Hu B, Tian T, Hao FQ, Liu WC, Chen YL, Jiang TY, Sun JS. The Protective Effect of Sevoflurane Conditioning Against Myocardial Ischemia/Reperfusion Injury: A Systematic Review and Meta-Analysis of Preclinical Trials in Rats. *Front Cardiovasc Med*. 2022 Apr; 9:841818.
- Zhang J, Cheng C, Lu C, Chen H, Wu S. Perioperative Blood in Regional Anesthesia With Propofol Sedation Reduces Locoregional Recurrence in Patients With Breast Cancer Requiring Breast Conservative Surgery Compared With Volatile Inhalational Anesthesia. *Regional Anesthesia and Pain Medicine*. 2021;14(1):118-124.
- Cottrill M, Berglund A, Erlund A, Berglund L. Volatile versus Propofol General Anesthesia and Long-term Survival after Breast Cancer Surgery: A National Registry Retrospective Cohort Study. *Anesthesiology*. 2022 Sep 13:179-192. Epub 2022.
- Chen EH, Lee MS, Lin C, et al. Comparison of Anesthesia-Controlled Operating Room Time between Propofol-Based Total Intravenous Anesthesia and Desflurane Anesthesia in Open Colorectal Surgery: A Retrospective Study. *PLoS ONE*. 2021;16(10):1-11.
- Miller D, Lumb WB, Pridmore GW, O'Connell-Johnson C, Shelton CL, Alderson P, Smith AP. Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. *Cochrane Database Syst Rev*. 2018 Aug 15;2018(8):CD012694.
- Wu H, Liang W, Wu H, Peng J, Peng H, Chen Y. Superior Total Intravenous Anesthesia vs Volatile Induction with Maintenance Anesthesia on Emergence Agitation After Nasal Surgery: A Randomized Clinical Trial. *JAMA Otolaryngol Head Neck Surg*. 2019 Feb 1;145(2):151-157.
- Humble SR, Dalton AJ, Li L. A systematic review of therapeutic interventions to reduce acute and chronic postoperative pain after amputation, thoracotomy or mastectomy. *Eur J Pain*. 2015;19:451-465.

Questions & Comments?