Opioid-free anesthesia

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Conflits d'intérêts: Abbvie, BBraun, Aspen

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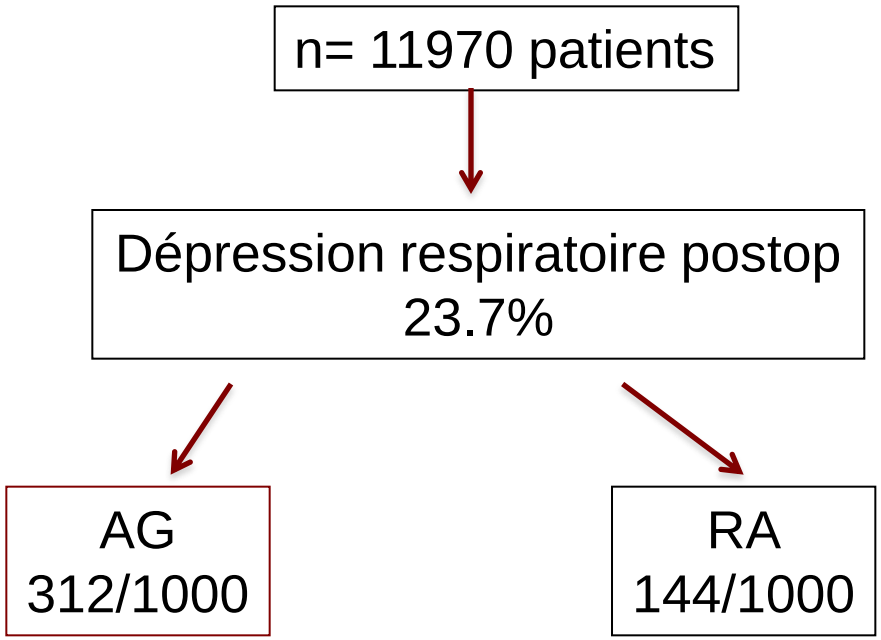
1960: Révolution
Opiacés de synthèse

- Réduction des agents hypnotiques
- Inhibition du système sympathique sans collapsus cardiovasculaire
- Limitation des réponses cardiovasculaires à un stimulus douloureux
- **<u>Stabilité hémodynamique</u>**
- Inhibition de la respiration spontanée

Hypoxémie postopératoire: quel rôle des morphiniques?



Risque augmente avec:

- Isoflurane
- Posologie des opiacés perop

Fdr:
Gabapentine preop
Oxycodone > 20 mg postop

Weingarten et al, RAPM 2015

Postoperative Opioid-induced Respiratory Depression
A Closed Claims Analysis

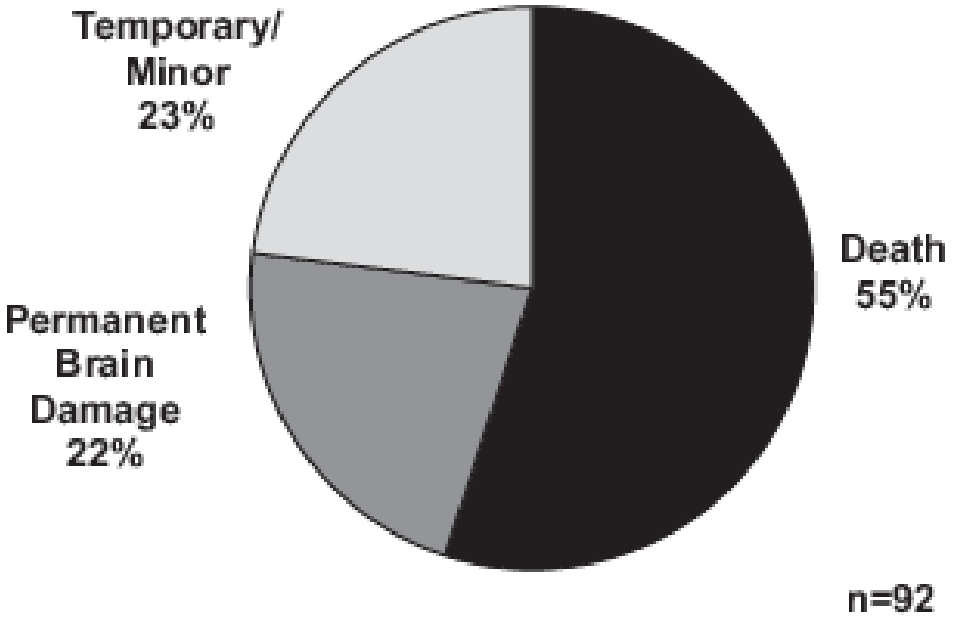
Lee L et al, Anesthesiology 2015

1990-2009

n = 357 acute pain claims

92 opioid-induced respiratory depression

88% within 24h after surgery



Opiacés = hyperalgésie

n = 1494, 27 études

Douleur EVA/100	Consommation morphine	Effets secondaires
SSPI: ↑ 9.4 mm CI [4.3-14.3] **H4 :** ↑ 6.6 mm [2.7-10.5] **H24 :** ↑3 mm [0.4-5.6]	**Titration** ↑**2.5 mg** **H24** ↑**18 mg**	**NVPO** RR 1.65 CI [0.8-1.3] **Sédation** RR 0.9 [0.6-1.5]

Martinez V et al, BJA 2014

Opiacés = chronicisation de la douleur postopératoire

n=38
Chirurgie thoracique
Remifentanil 5 ng/ml + APD postop *vs* Remifentanil 2 ng/ml + APD perop

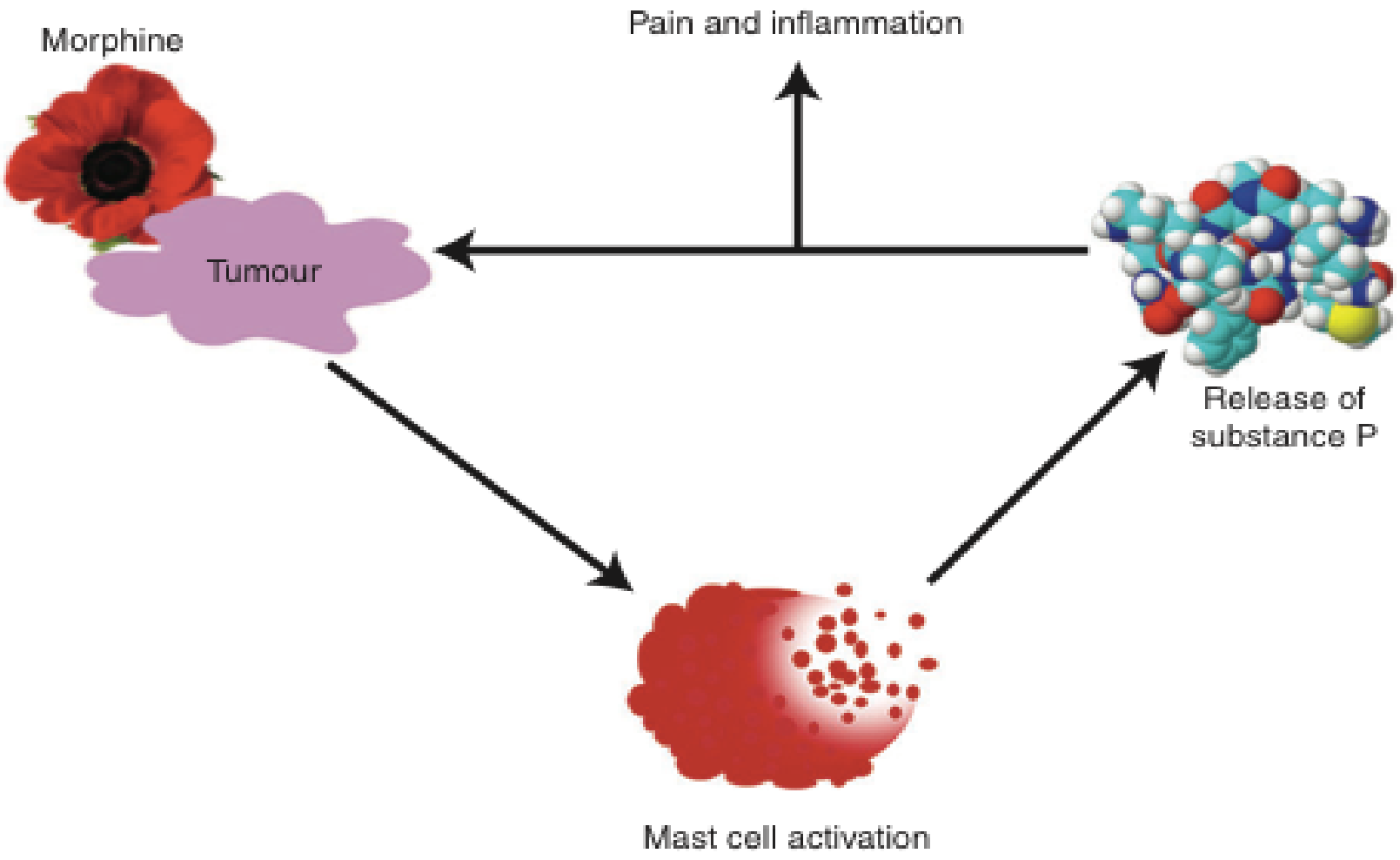
Table 3. Number of Patients with Pain

	High-Dose Group N = 20	Low-Dose Group N = 18	RR [95% CI]	*p* Value
1 month postop	16 (80%)	12 (66.7%)	1.2 [0.81-1.78]	0.364
3 months postop	15 (75%)	5 (27.8%)	2.7 [1.23-5.93]	0.013
6 months postop	16 (80%)	5 (27.8%)	2.9 [1.32-6.26]	0.008
End of study	14 (70%)	3 (16.7%)	4.2 [1.44- 12.27]	0.009

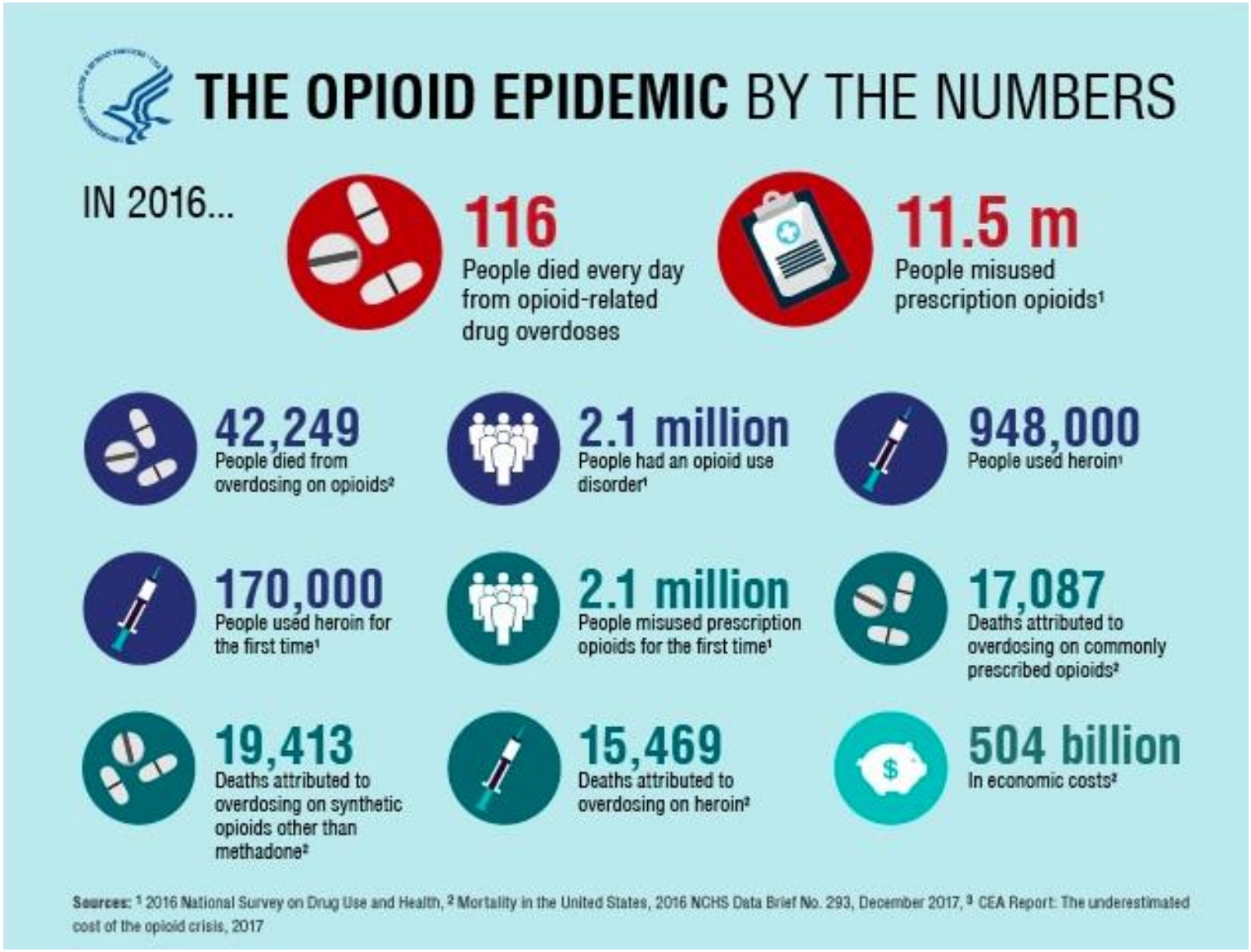
Salengros et al, J Cardiothorac Vasc Anesth 2010

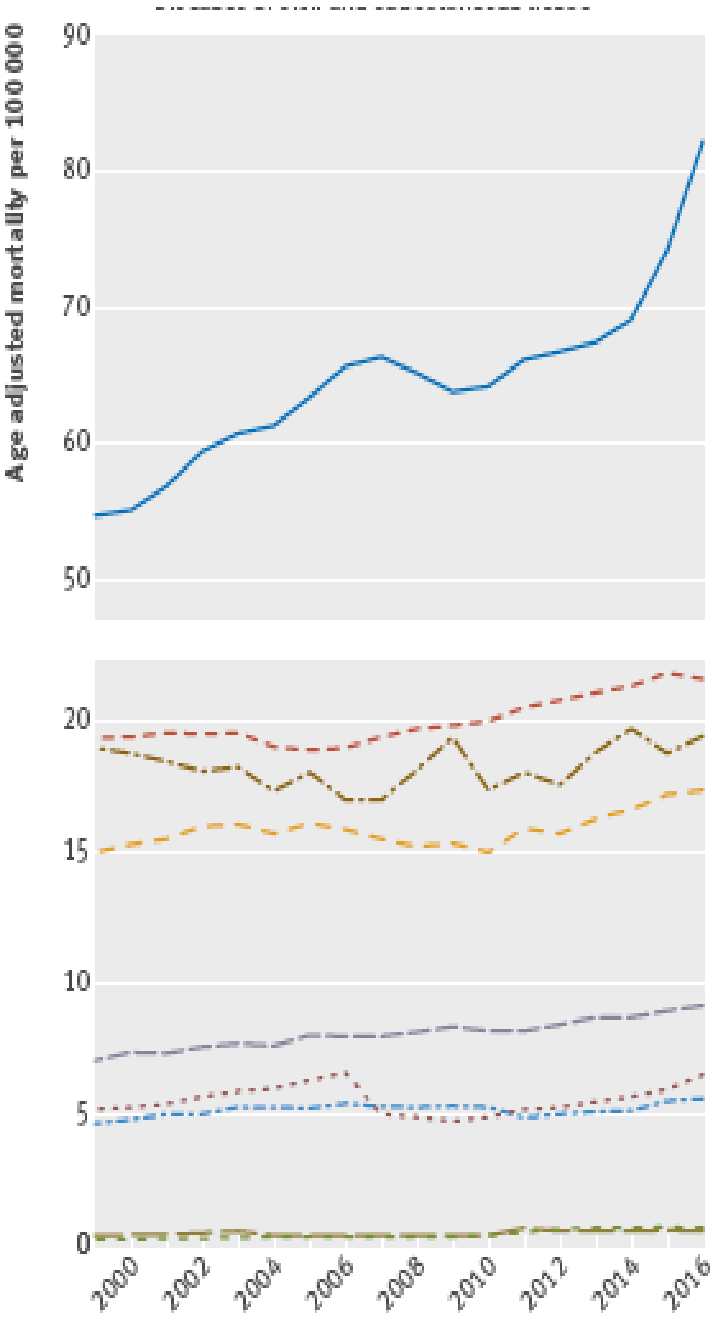
Morphine stimulates cancer progression and mast cell activation and impairs survival in transgenic mice with breast cancer

Nguyen J et al, BJA 2014



National Institute on Drug Abuse





Changes in midlife death rates across racial and ethnic groups in the United States: systematic analysis of vital statistics

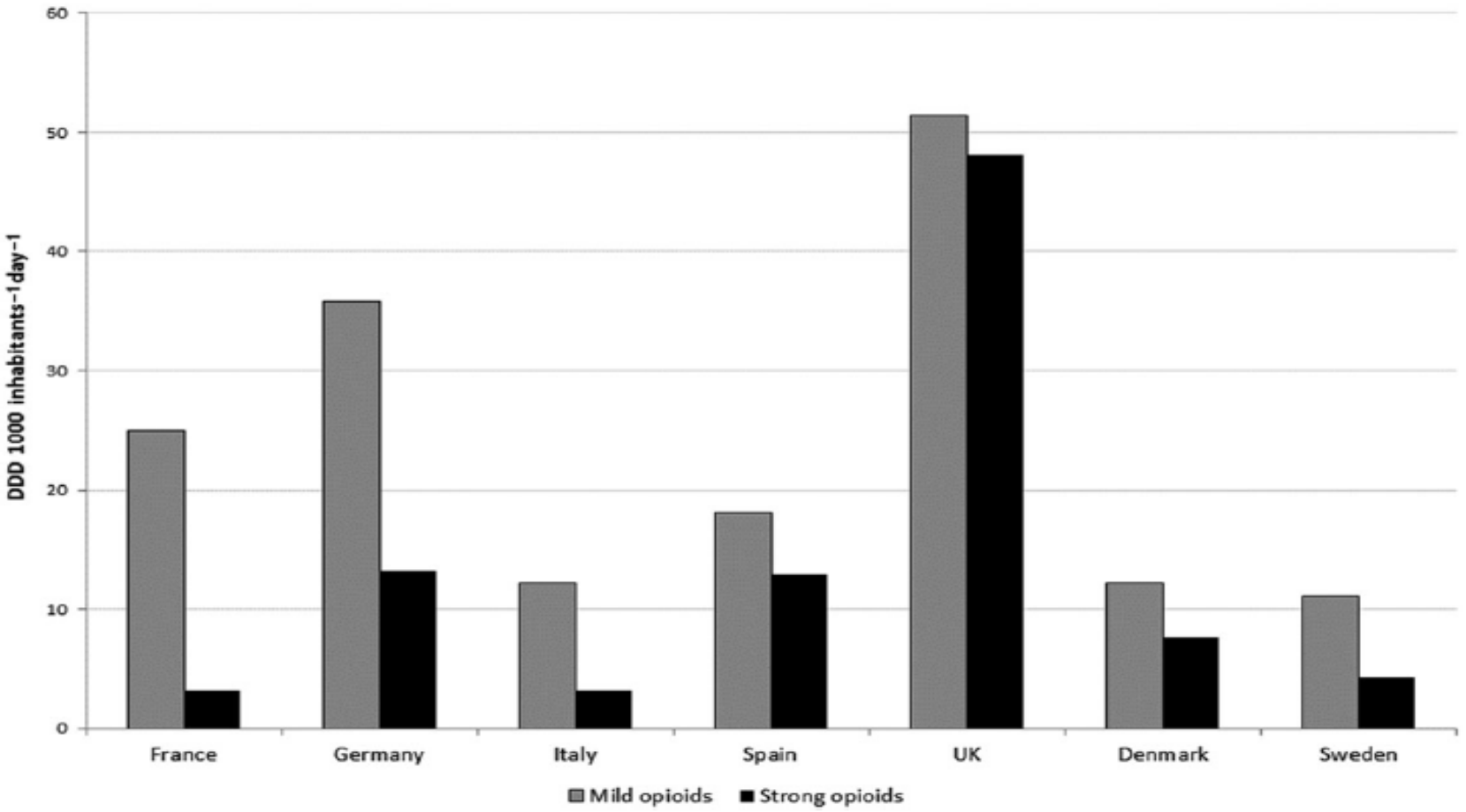
Woolf, BMJ 2018

L'espérance de vie aux USA raccourcit depuis 2014.

Ceci est lié à l'accroissement de la mortalité des 25-64 ans depuis 1999, secondaire aux overdoses

Trends in analgesic consumption in France over the last 10 years and comparison of patterns across Europe

Hider-Mlynark et al, Br J Clin Pharmacol 2018



Prescription opioid analgesic use in France: trends and impact on morbidity-mortality

Chenaf et al, EJP 2018

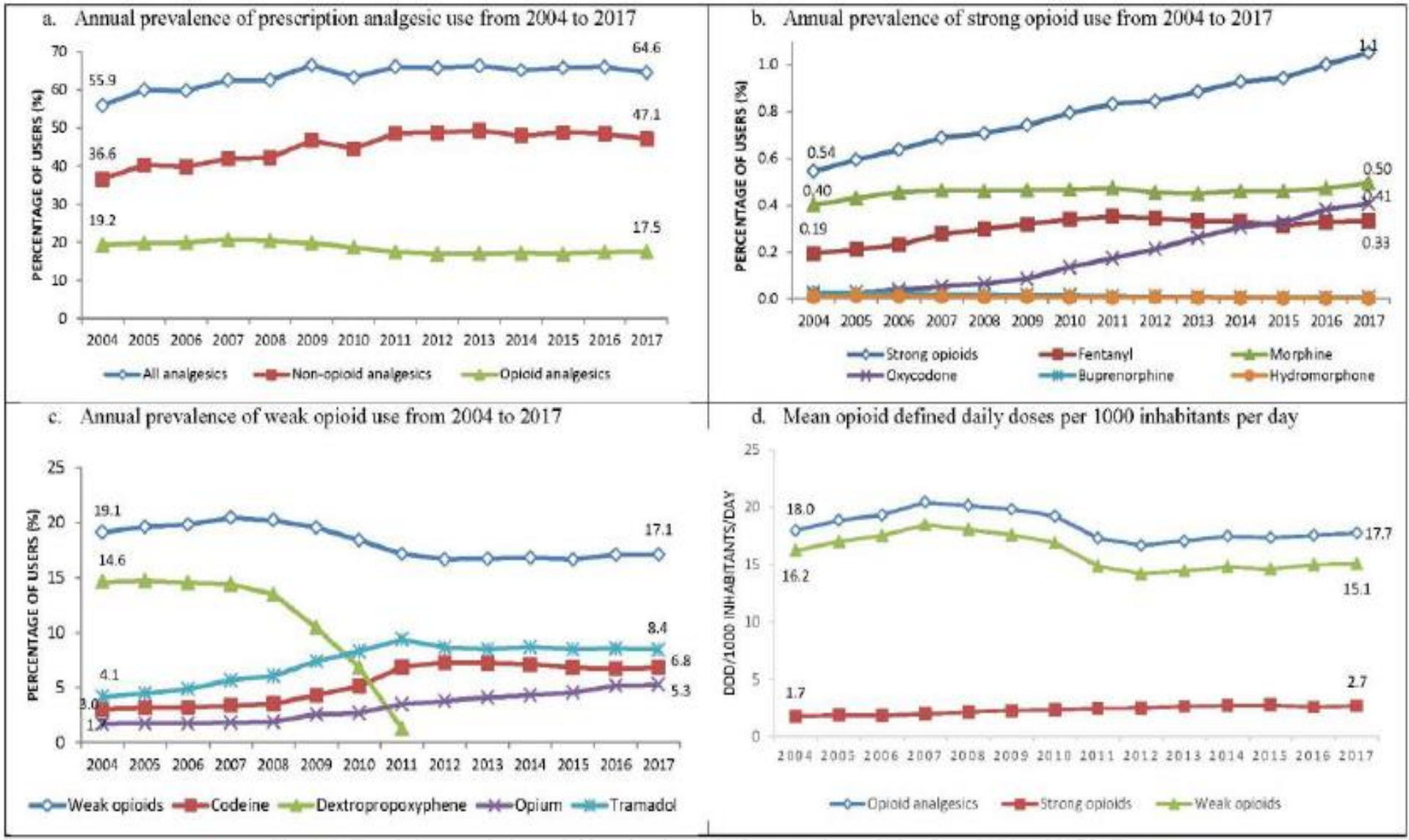
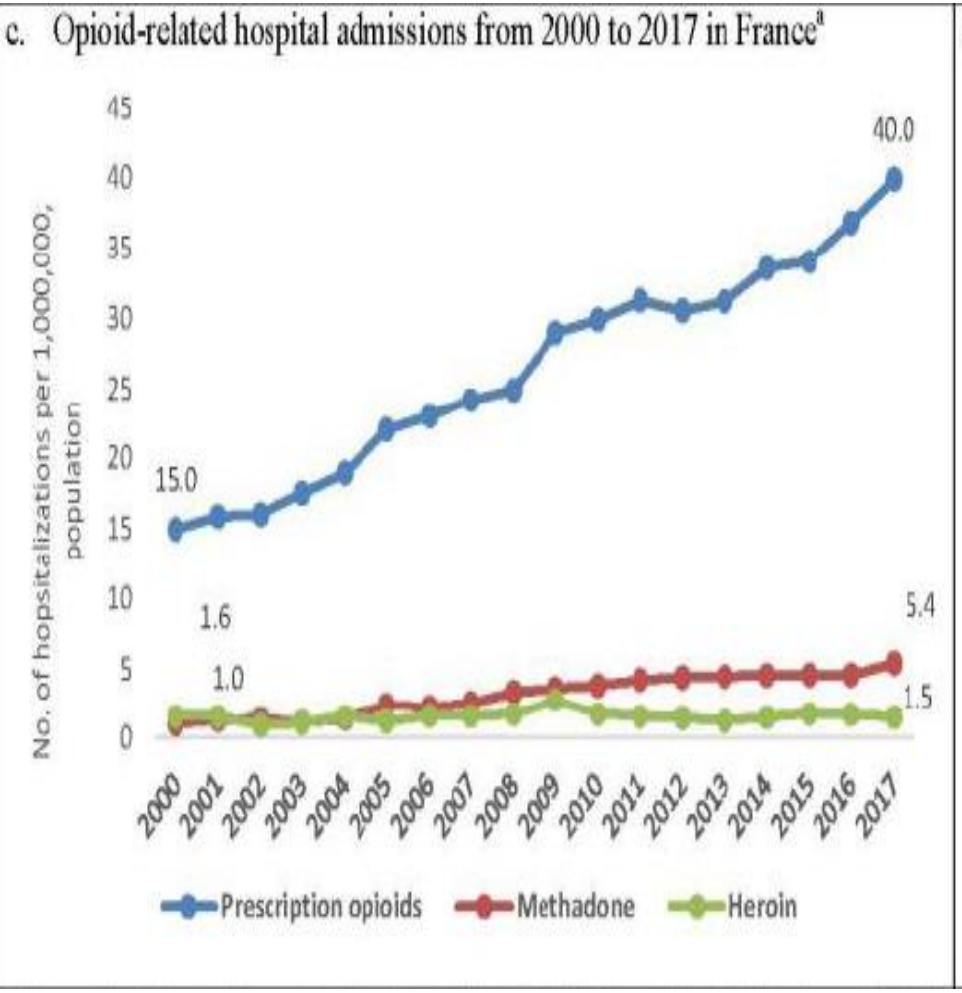
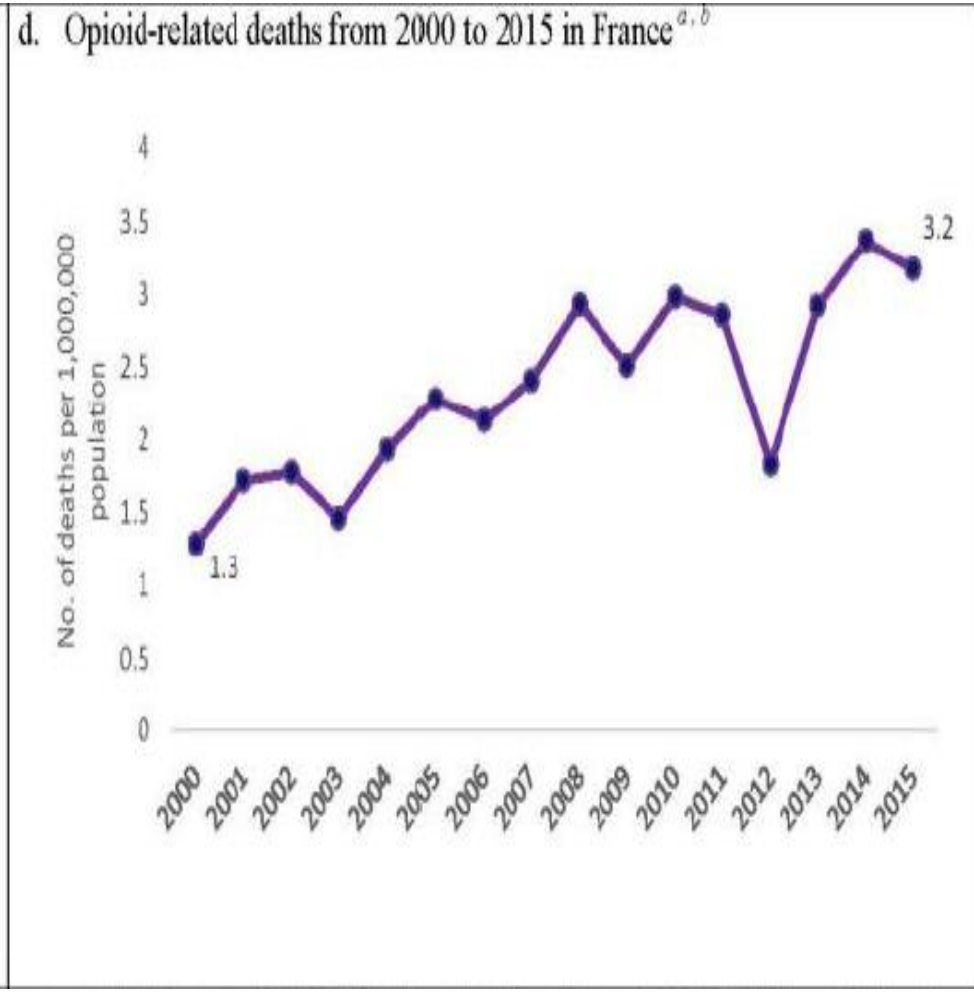


Figure 1. Trends in prescription opioid analgesic use in the general population from 2004 to 2017 in France

Prescription opioid analgesic use in France: trends and impact on morbidity-mortality

Chenaf et al, EJP 2018





“Houston, We Have a Problem!”:
The Role of the Anesthesiologist in the Current Opioid Epidemic

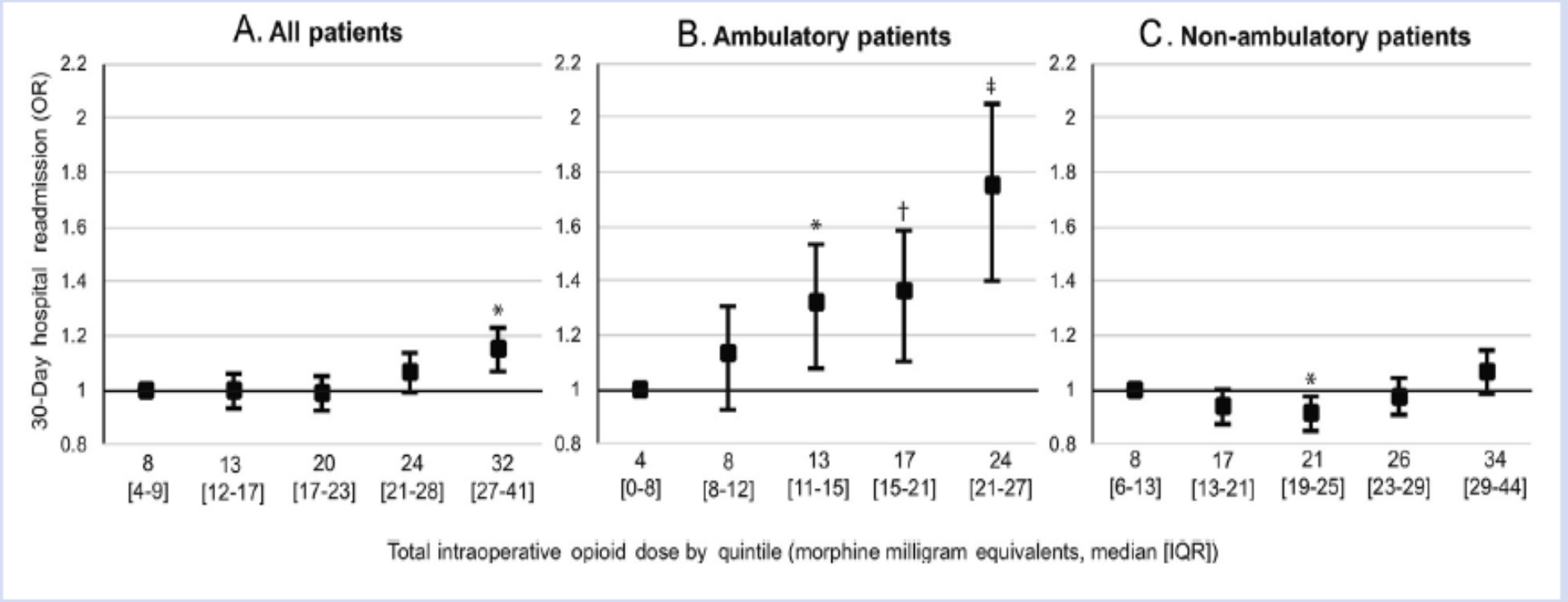
Yaster, Anesth Analg 2017

La notion selon laquelle les patients douloureux sous opiacés n’ont pas d’addiction repose sur un éditorial (Porter, Nejm 1980) et une étude sur 38 patients douloureux chronique (Portenoy, Pain 1986)

Association between intraoperative opioid administration and 30-day readmission: a pre-specified analysis of registry data from a healthcare network in New England

Long et al. BJA 2018

Association entre opiacés perop et réadmission à J30
Registre américain
153 902 patients



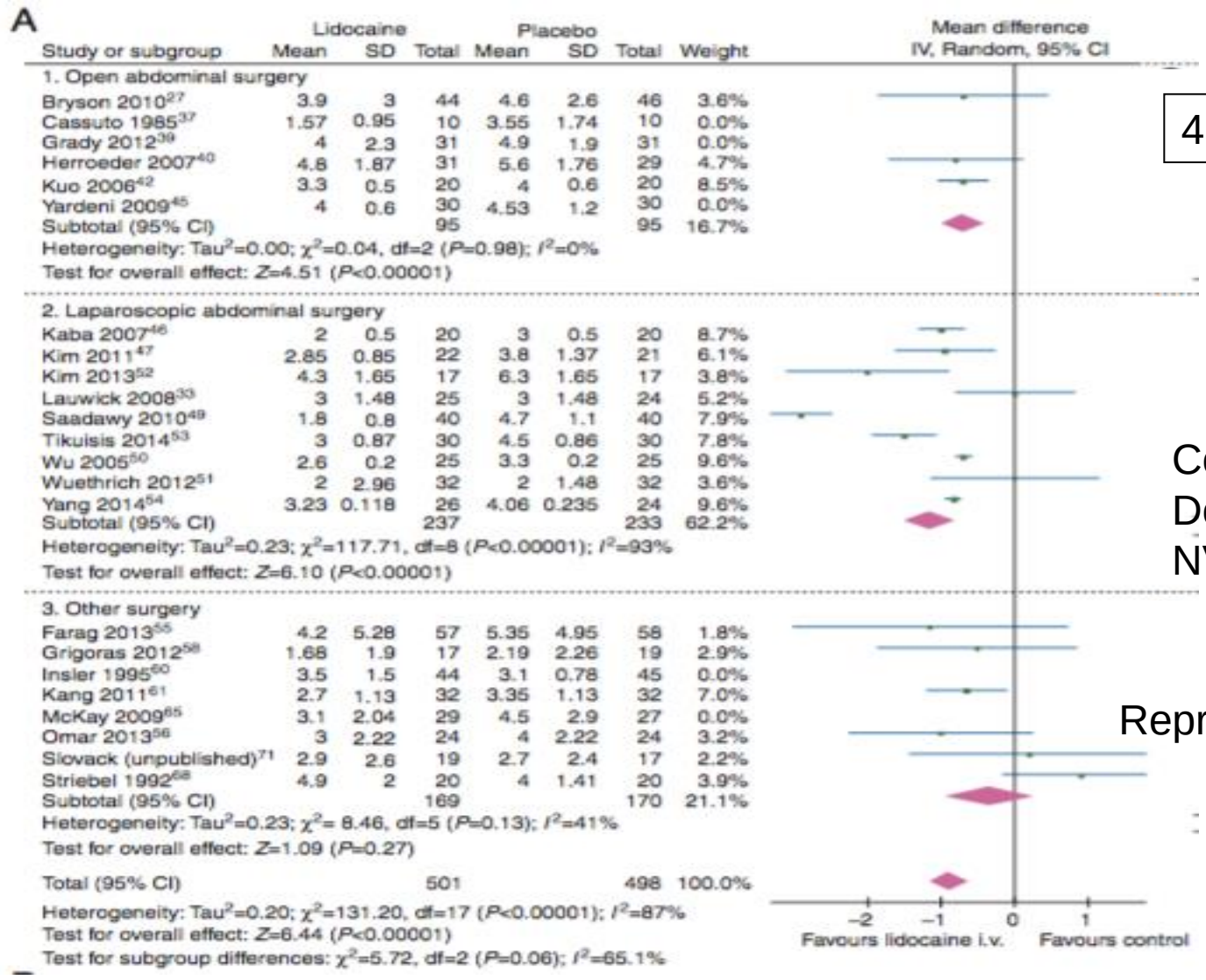
Comment éviter les opiacés en peropératoire?

ANESTHESIE MULTIMODALE

- ALR et ALs (lidocaine IV)
- Antagonistes NMDA : kétamine
- Magnésium
- Anti-inflammatoires: NSAID, dexaméthasone
- Inhibiteurs du système sympathique : alpha 2 agonistes

Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis

Weibel et al, BJA 2016



45 études, 2802 patients

Consommation morphine
Douleur à H24
NVPO

Reprise du transit accélerée

A systematic review of intravenous ketamine for postoperative analgesia

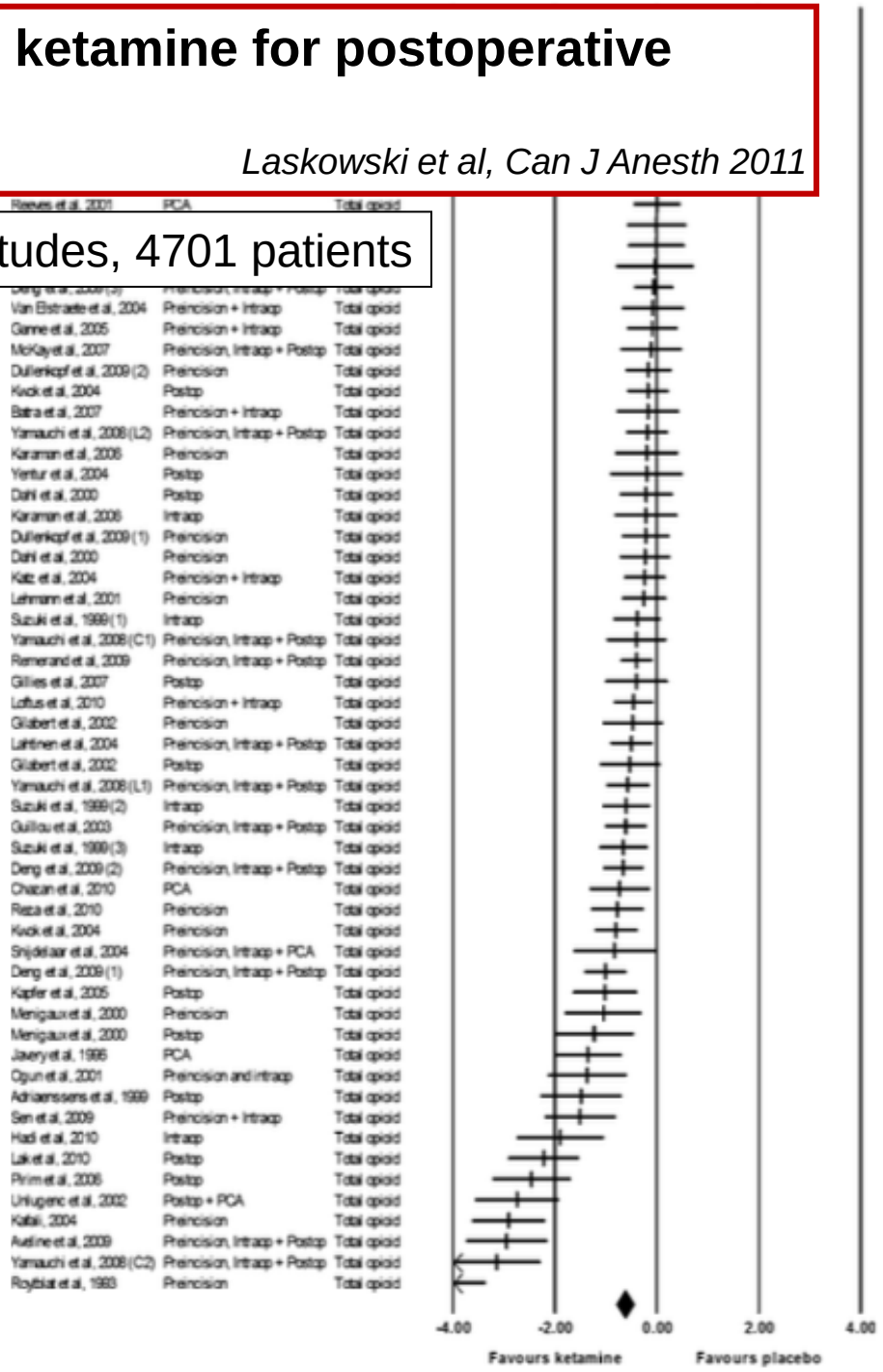
Laskowski et al, Can J Anesth 2011

91 comparaisons, 70 études, 4701 patients

- Réduction de la consommation d'opiacés et de la douleur postop
- Chir abdo, thoracique et ortho majeure ++

- Plus d'hallucinations/cauchemars
- Réduction NVPO

- Indépendant de la dose et de l'administration

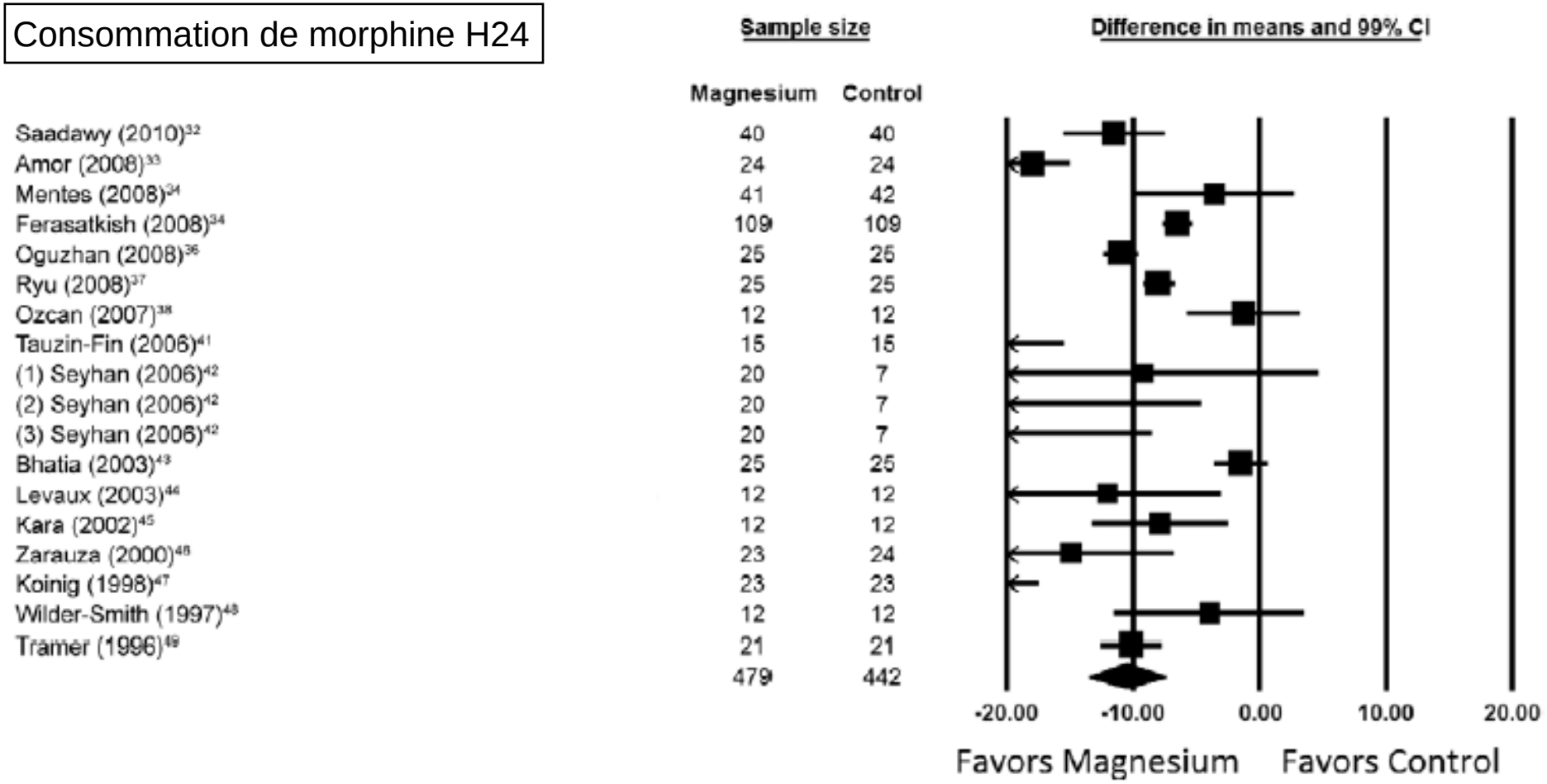


Perioperative systemic magnesium to minimize postoperative pain

De Oliveira et al, Anesthesiology 2013

20 études, 1257 patients

Consommation de morphine H24



Stable anesthesia with alternative to opioids: Are ketamine and magnesium helpful in stabilizing hemodynamics during surgery? A systematic review and meta-analyses of randomized controlled trials

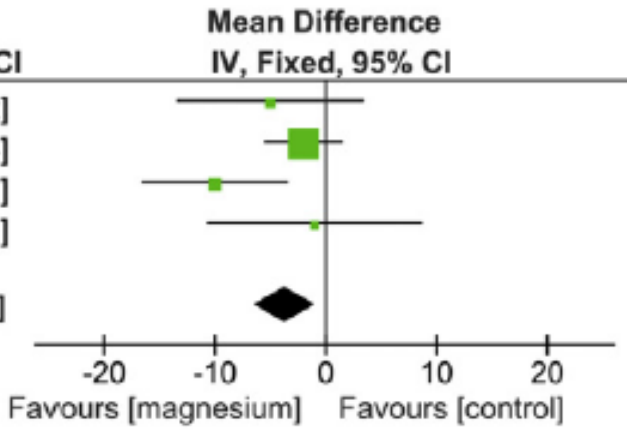
Forget P et al, Best Pract & Res Clin Anaesth 2017

6 études, 292 patients

Variabilité de la fréquence cardiaque

	Magnesium			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Altan 2005	5	12	20	10	15	20	11.1%	-5.00 [-13.42, 3.42]
Elsharnouby 2006	22	7	30	24	7	30	62.7%	-2.00 [-5.54, 1.54]
Jee 2009	2	9	17	12	10	15	17.9%	-10.00 [-16.63, -3.37]
Ryu 2008	18	17	25	19	18	25	8.3%	-1.00 [-10.71, 8.71]
Total (95% CI)			**92**			**90**	**100.0%**	**-3.68 [-6.49, -0.88]**

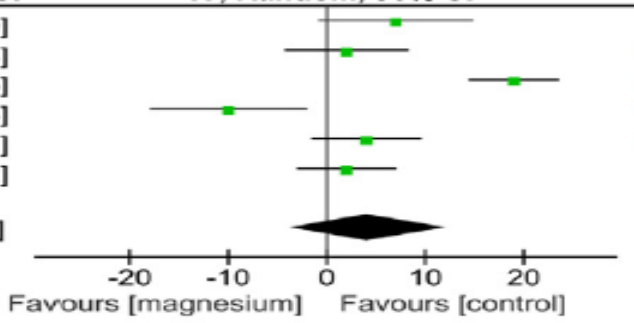
Heterogeneity: Chi² = 4.75, df = 3 (P = 0.19); I² = 37%
Test for overall effect: Z = 2.57 (P = 0.01)



Variabilité de la pression artérielle

	Magnesium			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Altan 2005	22	10	20	15	15	20	15.7%	7.00 [-0.90, 14.90]
Cizmeci 2007	19	13	30	17	12	30	16.7%	2.00 [-4.33, 8.33]
Elsharnouby 2006	37	9	30	18	9	30	17.6%	19.00 [14.45, 23.55]
Jee 2009	9	12	17	19	11	15	15.6%	-10.00 [-17.97, -2.03]
Mahmoud 2016	6	11	25	2	9	25	17.1%	4.00 [-1.57, 9.57]
Ryu 2008	29	8	25	27	10	25	17.4%	2.00 [-3.02, 7.02]
Total (95% CI)			**147**			**145**	**100.0%**	**4.24 [-3.55, 12.03]**

Heterogeneity: Tau² = 84.39; Chi² = 51.21, df = 5 (P < 0.00001); I² = 90%
Test for overall effect: Z = 1.07 (P = 0.29)



Dexmédétomidine

Agoniste très sélectif (1 300 fois plus que la clonidine) des récepteurs α2-adrénergiques: bloc sympathique direct

Pharmacocinétique: distribution rapide (tL/2α = 6 min, clonidine 20 min), demi-vie d'élimination: 2 h (clonidine 12 à 16h), fortement lié aux protéines plasmatiques, métabolisé par le foie en un composé inactif.

Pharmacodynamie: pas d'affinité forte pour aucun autre type de récepteur.

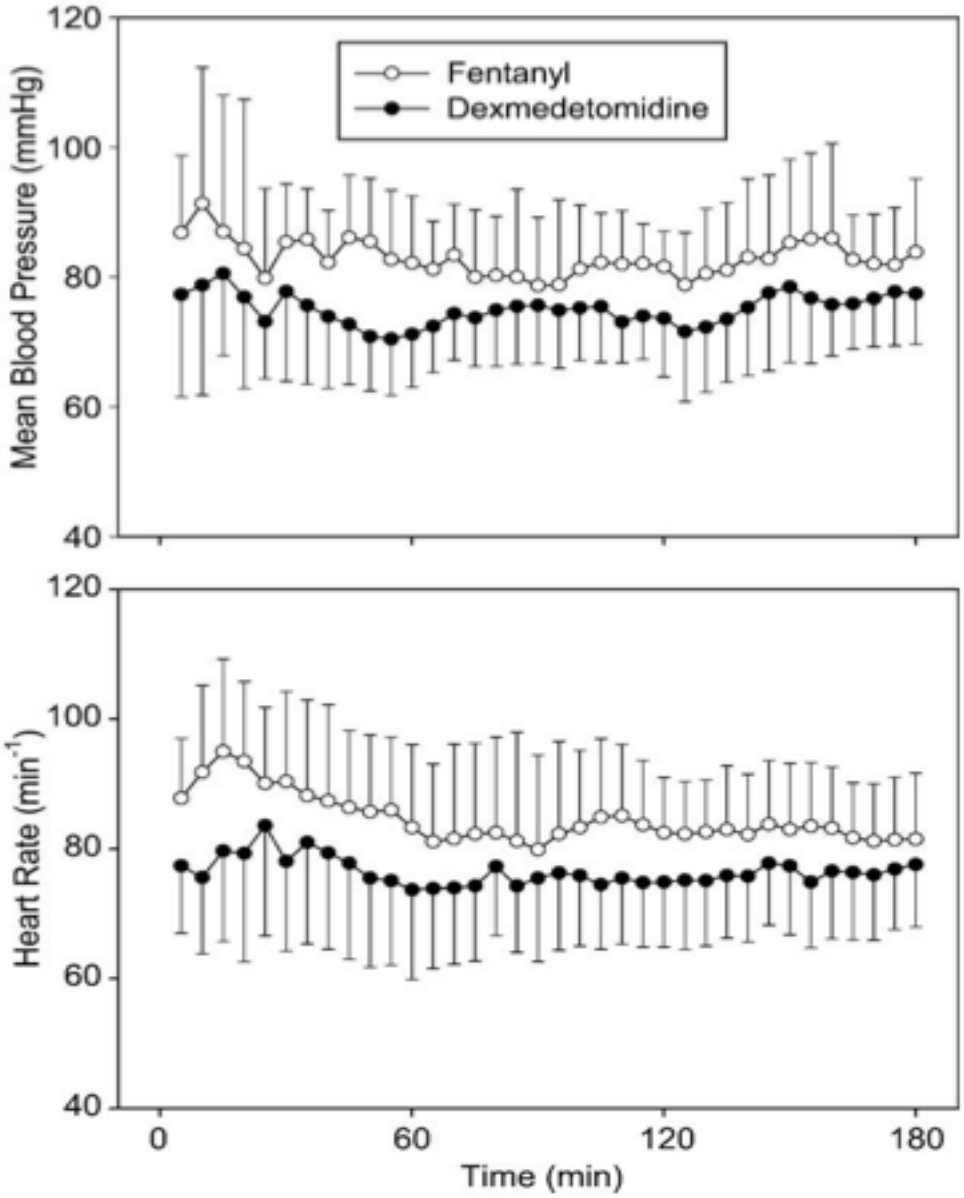
SNC: hypnose, sédation, anxiolyse et analgésie.

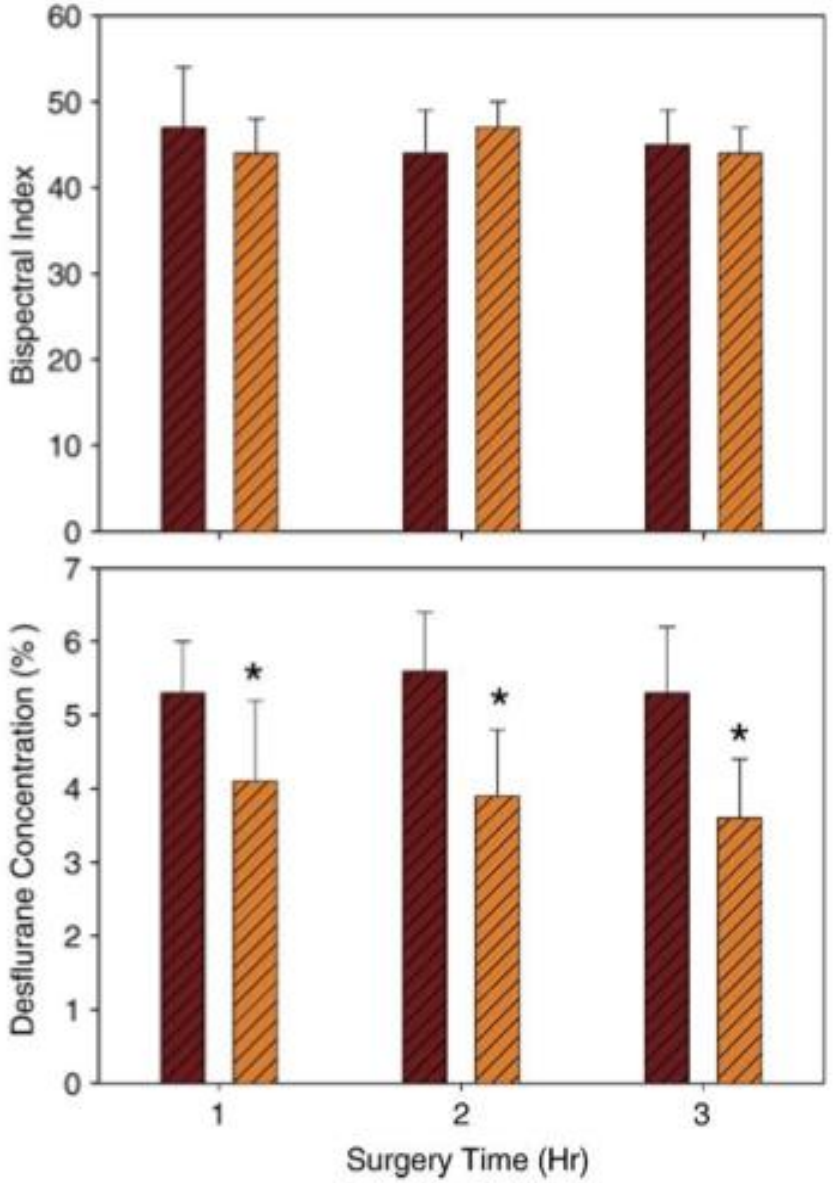
Cardiovasculaire: action biphasique et prédictible: élévation initiale transitoire de la PA (stimulation de récepteurs α2musculaires) puis baisse modérée de la PA et de la FC qui sont la conséquence directe de ses propriétés sympatholytiques.

Efficacité analgésique est identique à la clonidine mais son profil « risque-bénéfice » pourrait être différent (pharmacocinétique différente)

Fentanyl or dexmedetomidine combined with desflurane for bariatric surgery

Feld et al, J clin Anesth 2006





Fentanyl or dexmedetomidine combined with desflurane for bariatric surgery

Feld et al, J clin Anesth 2006

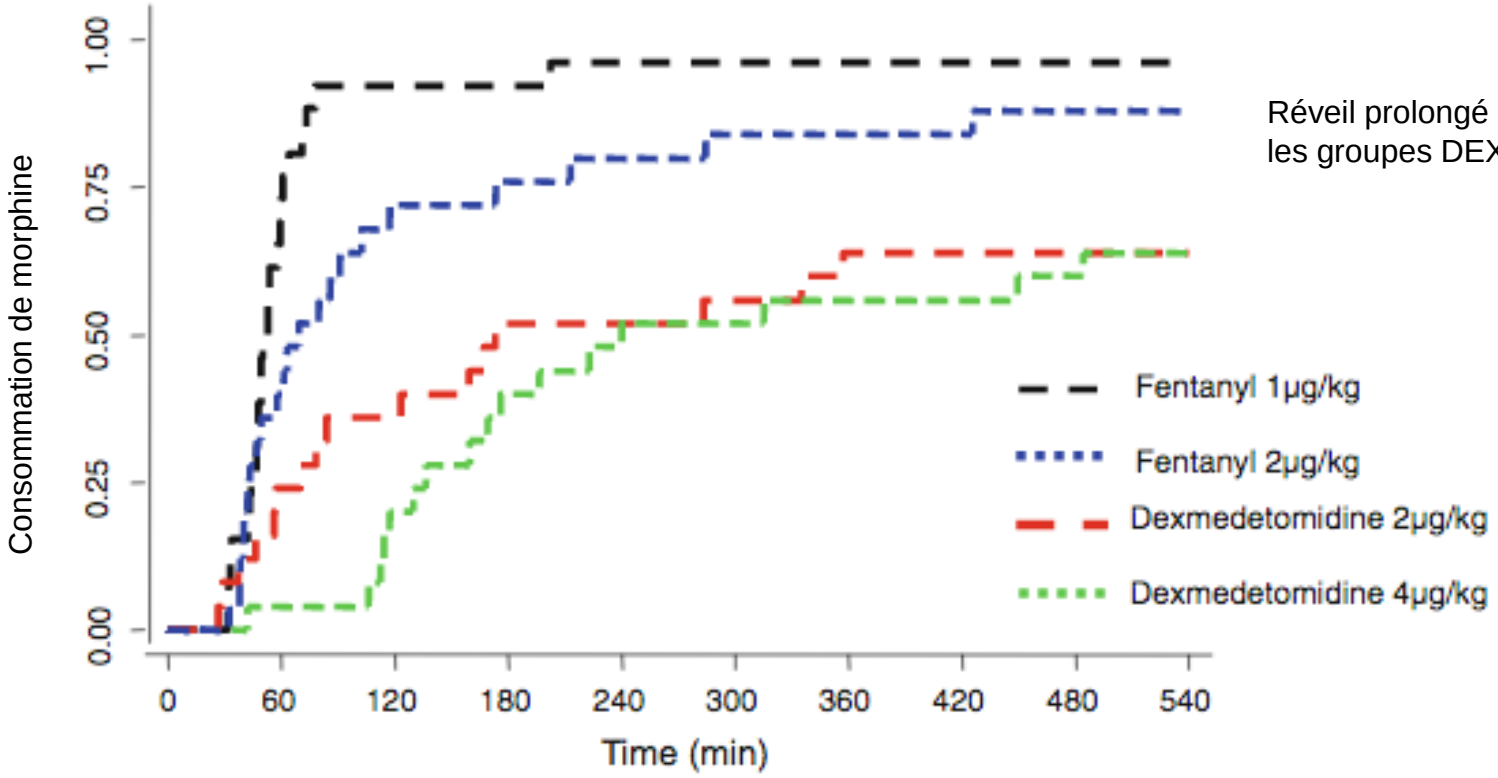
Table 2 Measurements made at the end of surgery in the PACU

	Fentanyl	Dexmedetomidine
Duration of surgery (min)	229 ± 30	234 ± 28
End of surgery to extubation (min)	14.2 ± 6.6	9.4 ± 2.7*
PACU pain score (0-10, 1 h)	7 (5.25-8.75)	3.5 (0-5.0)*
PACU pain score (0-10, 2 h)	6.0 (5.0-7.0)	2.0 (2.0-3.5)*
PACU morphine (mg, 2 h)	14.6 ± 5.9	6.1 ± 3.5*
PACU mean blood pressure (mm Hg, 1 h)	89 ± 12	77 ± 9*
PACU heart rate (min^{-1}, 1 h)	94 ± 13	75 ± 5*

High-dose dexmedetomidine increases the opioid-free interval and decreases opioid requirement after tonsillectomy in children

Pestieau et al, CJA 2011

Amydalectomie
26 patients / groupe



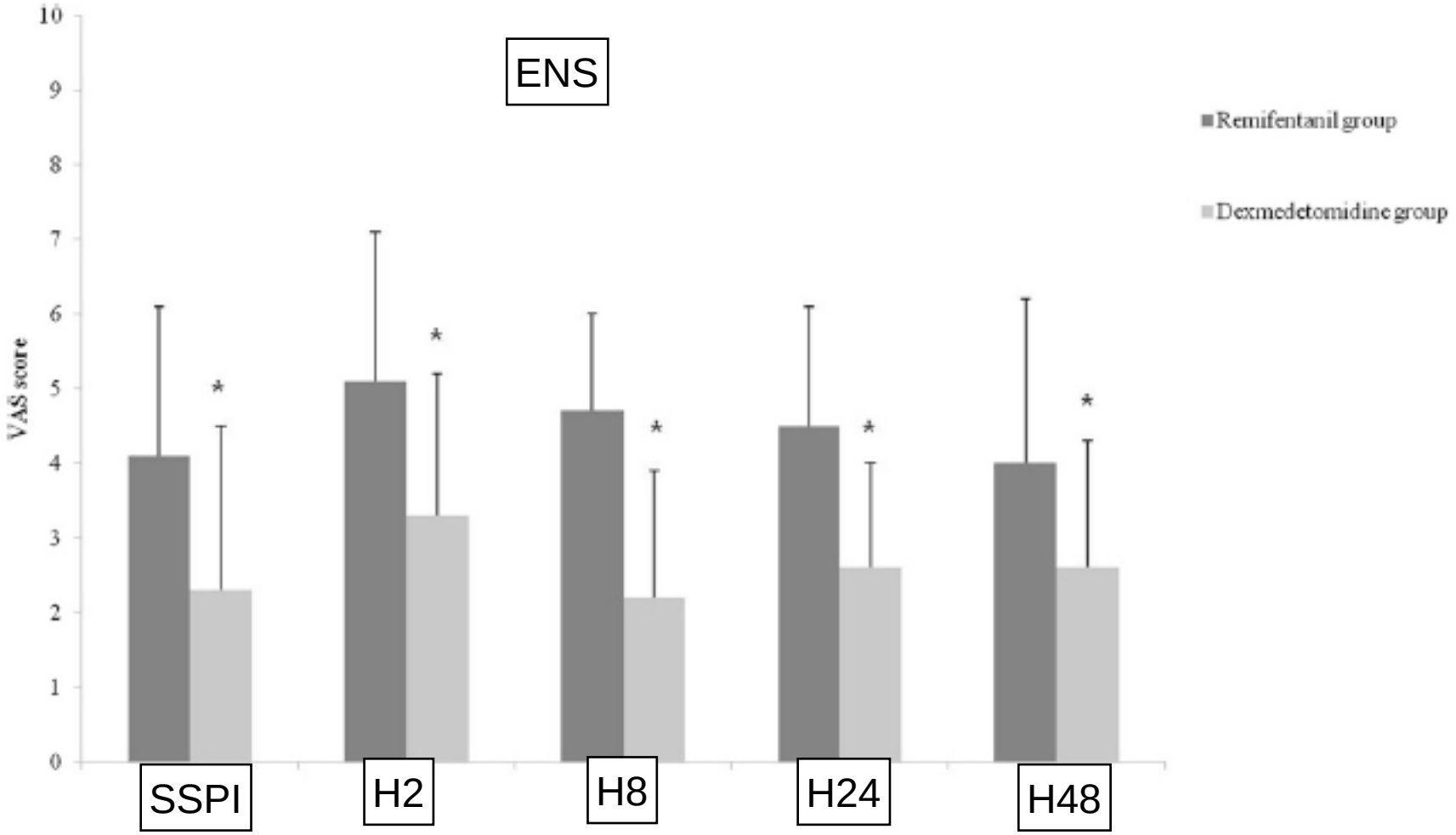
Réveil prolongé dans les groupes DEX

Dexmedetomidine versus remifentanil in postoperative pain control after spinal surgery: a randomized controlled study

Hwang et al, BMC Anesthesiol 2015

40 patients

Dex vs remifentanil perop



Dexmedetomidine versus remifentanil in postoperative pain control after spinal surgery: a randomized controlled study

Hwang et al, BMC Anesthesiol 2015

40 patients
Dex vs remifentanil perop

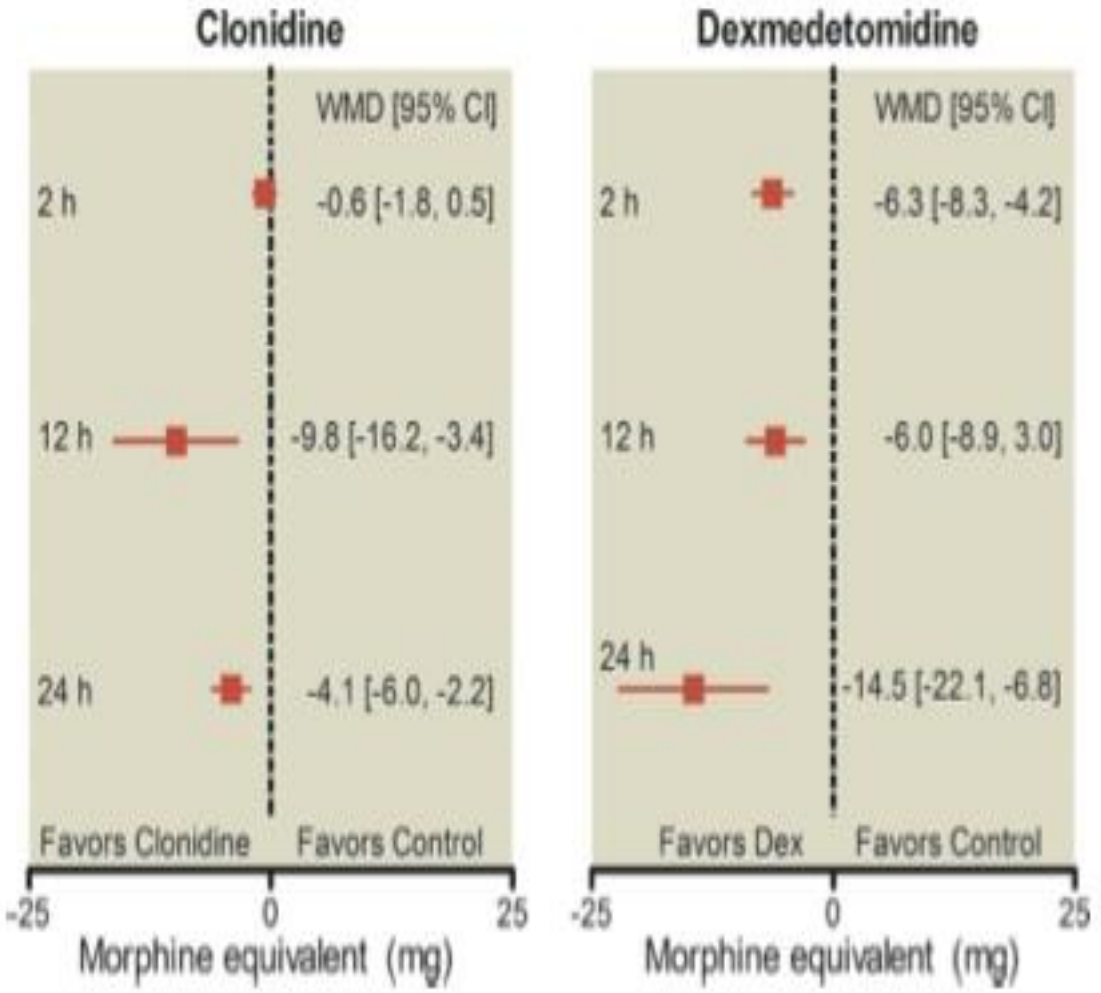
	Remifentanil group	Dexmedetomidine group	*P*-value
Incidence of rescue analgesics (*n*)			
Postoperative 2 h (%)	4 (22.2)	0 (0)	0.046
Postoperative 8 h (%)	9 (50)	3 (15.8)	0.038
Postoperative 24 h (%)	10 (55.6)	4 (21.1)	0.045
Postoperative 48 h (%)	9 (50)	3 (15.8)	0.038
Incidence of PONV (*n*)			
Postoperative 2 h (%)	6 (33.3)	0 (0)	0.008
Postoperative 8 h (%)	8 (44.4)	2 (10.5)	0.029
Postoperative 24 h (%)	6 (33.3)	0 (0)	0.008
Postoperative 48 h (%)	2 (11.1)	0 (0)	0.230

Effect of Perioperative Systemic alpha2 Agonists on Postoperative Morphine Consumption and Pain Intensity

Systematic Review and Meta-analysis of Randomized Controlled Trials

Blaudszun G et al, Anesthesiology 2012

1792 patients



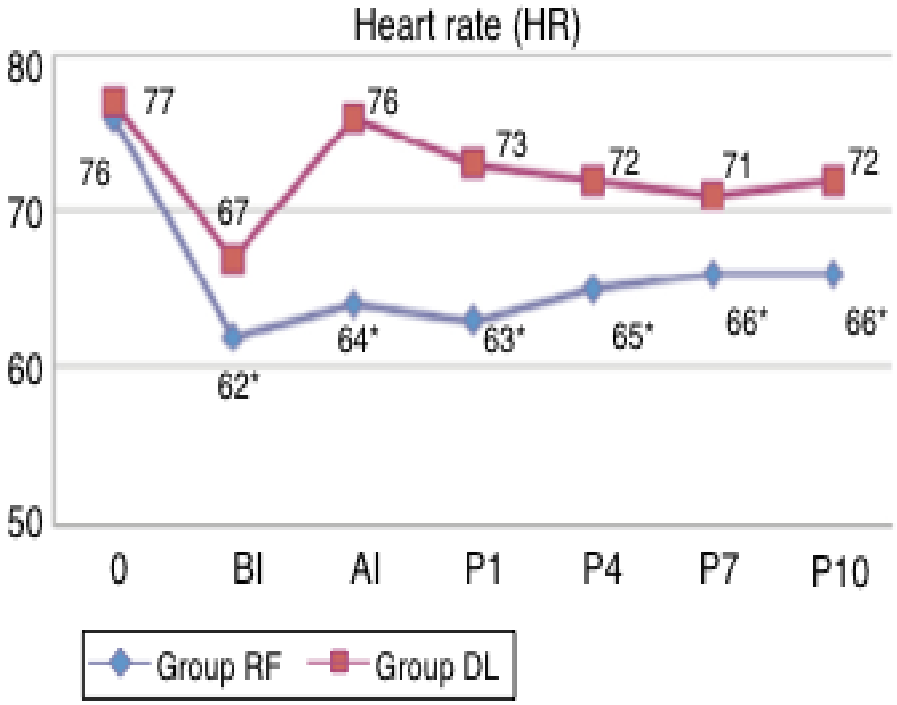
DEX: ↘ extubation delay
DEX et CLO: ↘ PONV

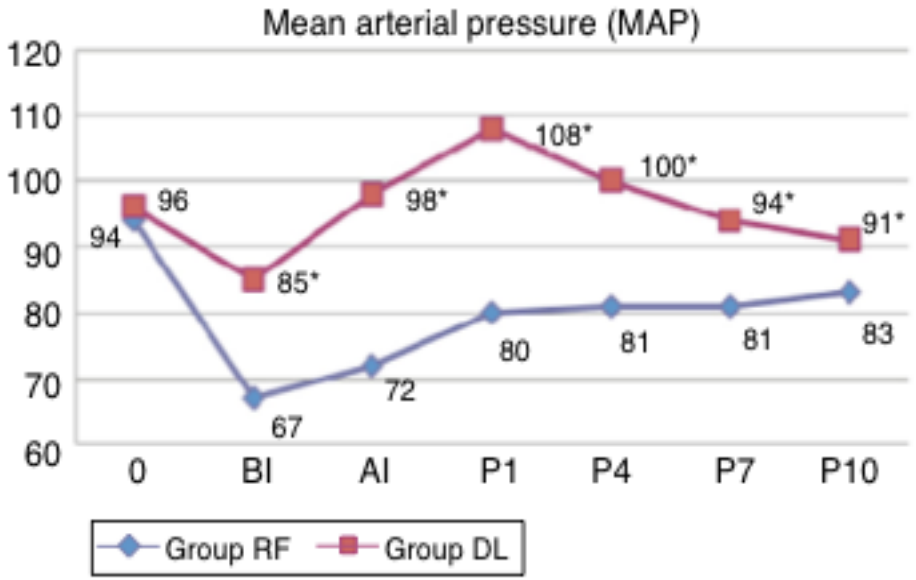
DEX: bradycardia
CLO: Hypotension

Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study

Bakan et al, Rev Bras Anesthesiol 2014

DEX + lido + propofol (n= 40)
Vs
Fentanyl and remifentanil + propofol (n= 40)



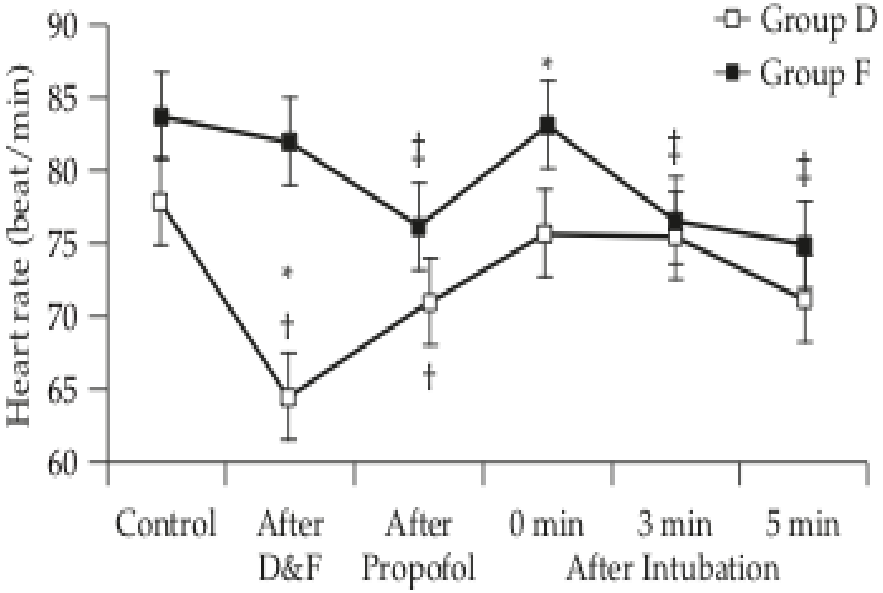


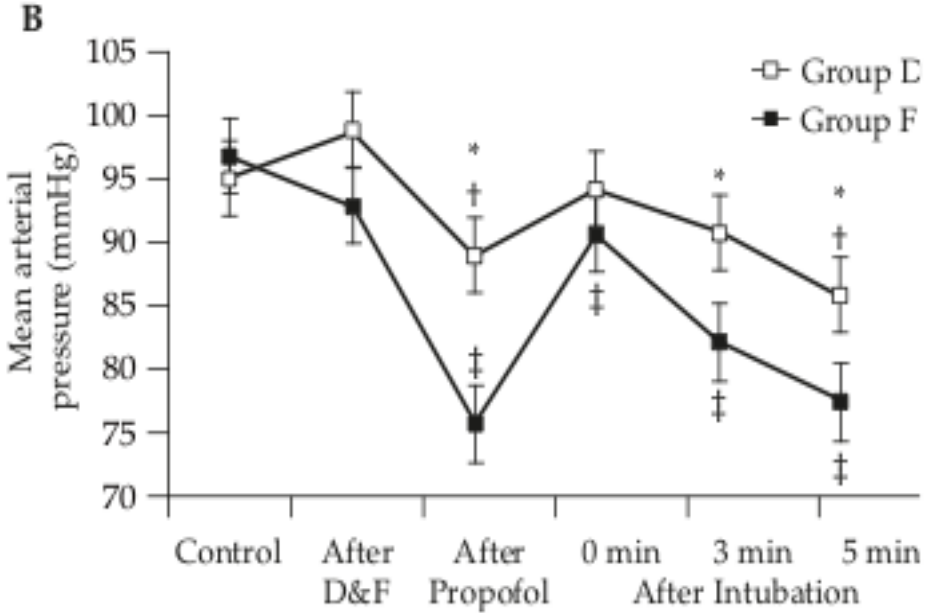
Effects of fentanyl-lidocaine-propofol and dexmedetomidine-lidocaine-propofol on tracheal intubation without use of muscle relaxants

Hanci et al, Kaohsiung J Med Sci 2010

DEX + lido + propofol (n= 30)
vs
Fentanyl+ lido + propofol (n= 30)

= > meilleures conditions d'IOT avec DEX





British Journal of Anaesthesia 112 (5): 906–11 (2014)
Advance Access publication 18 February 2014 · doi:10.1093/bja/aet551

BJA

Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis

P. Ziemann-Gimmel*, A. A. Goldfarb, J. Koppman and R. T. Marema

AG (Halogénés + opiacés)	TIVA (propofol + ketamine + dex)
37 %	20 %

- Apfel score identique dans les 2 groupes
- Reduction NVPO : 17,3 %
- Reduction de la sévérité des NVPO

A Randomized Controlled, Double-Blind Trial Evaluating the Effect of Opioid-Free Versus Opioid General Anaesthesia on Postoperative Pain and Discomfort Measured by the QoR-40

Mulier et al, J Clin Anesth Pain Med 2018

N= 50, étude randomisée, chirurgie bariatrique

OA (propofol, rocuronium, sufentanil) vs OFA (propofol, rocuronium, dex, lido, keta)

	OA (22)	**OFA (23)**
Sp02 < 94 % avec oxygène	11/11	2/21 *
NVPO	14/7	3/20*
ENS	4,9 (0,8)	1,7 (0,9) *
Morphine (mg) en SSPI	15,3 (7,1)	4,9(2,1)*
Morphine (mg) J1	18,2 (5,6)	14,7(4,7)
Qo40 score %	74(6)	89(3)*

- 39 ans
- Chirurgie bariatrique coelioscopique
- IMC 62
- Hypertension, diabète
- IOT difficile prévue

Intubation: vigile (fibroscope) avec DEX + anesthésie locale

AG: propofol et sevoflurane , DEX, rocuronium, (lido IV, Ketamine)

BIS entre 40 and 60, hémodynamique peropératoire stable

Postop: AINS, paracétamol, sugammadex

ENS = 4/10, NVPO = 0, score aldrete max 10 min après extubation, pas de mémorisation

Gaszynski T et al, Drug, Design, Development & Therapy, 2014

OFA = anesthésie 3.0 ?

Sécurité?

Effets hémodynamiques de la Dex

Comment?

Monitorage de la profondeur de l'anesthésie, de l'analgésie…

Preuves?

- Réduction des consommations de morphine?
- Réhabilitation améliorée?
- Réduction de l'hyperalgésie et de la chronicisation de la douleur postop ?

Quels patients?

- Obèses, insuffisant respiratoires ?
- Chirurgie carcinologique?
- Patients traités au long cours par opiacés?

PHRC 2016

Open access Protocol

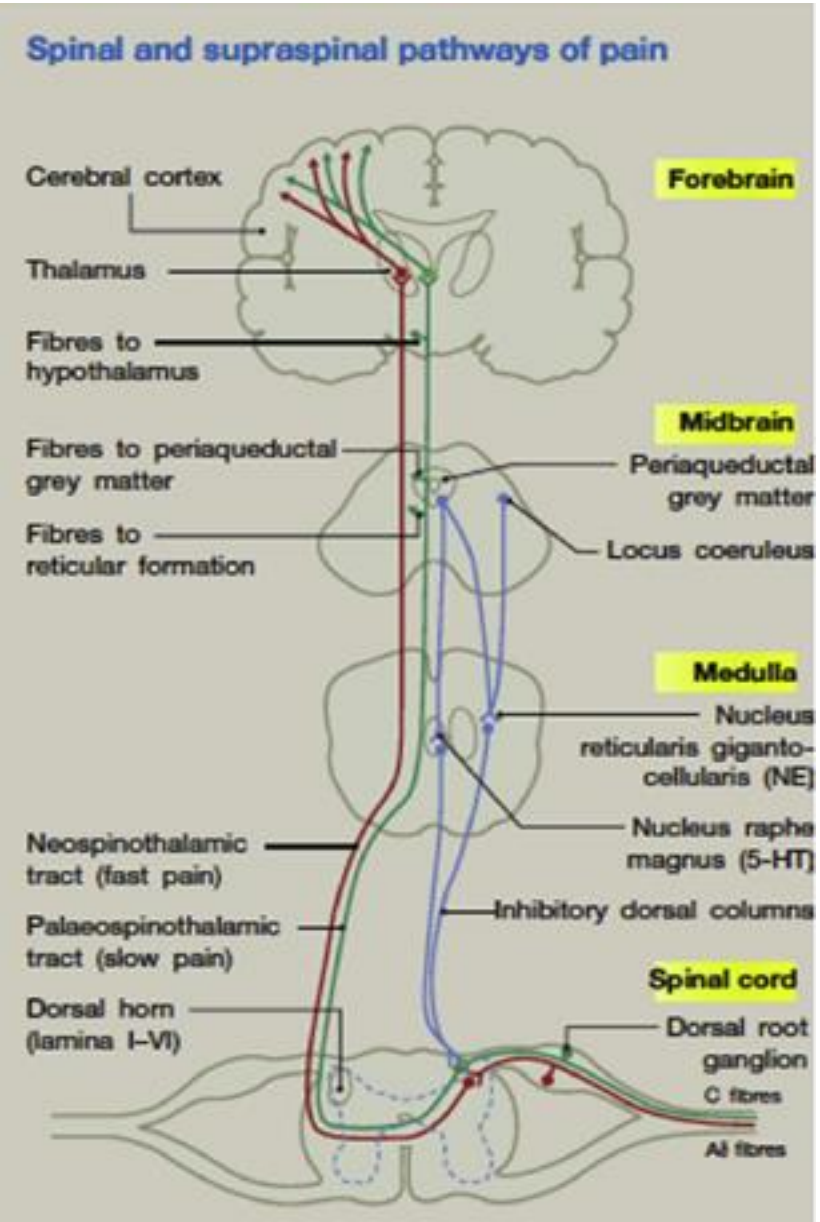
BMJ Open

POFA trial study protocol: a multicentre, double-blind, randomised, controlled clinical trial comparing opioid-free versus opioid anaesthesia on postoperative opioid-related adverse events after major or intermediate non-cardiac surgery

Helene Beloeil,[1] Bruno Laviolle,[2] Cedric Menard,[3,4] Catherine Paugam-Burtz,[5] Matthias Garot,[6] Karim Asehnoune,[7] Vincent Minville,[8] Philippe Cuvillon,[9] Sebastien Oger,[10] Julien Nadaud,[11] Sylvain Lecoeur,[12] Gerald Chanques,[13] Emmanuel Futier,[14] On behalf of the SFAR research network

Do we feel pain during anesthesia? A critical review on surgery-evoked circulatory changes and pain perception

Cividjian et al. Best Pract & Res Clin Anaesh 2017



Ne pas confondre douleur nociception

il est possible d'avoir une nociception (traumatisme) sans douleur et vice versa

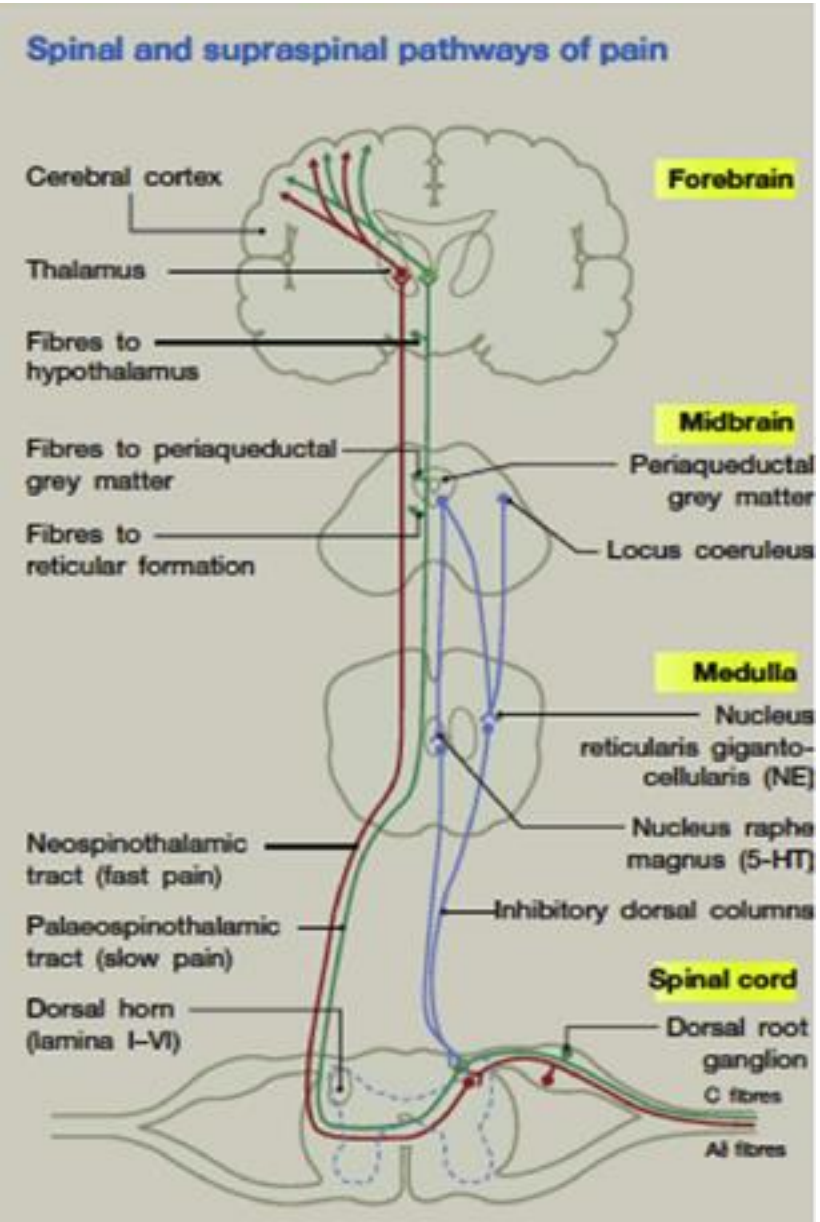
La douleur est une perception désagréable consciente d'un stimulus nociceptif

La nociception est la stimulation de récepteurs nociceptifs
L'anti-nociception est la suppression des conséquences de la stimulation des récepteurs nociceptifs

Sous AG: pas de de douleur mais de la noception!

Do we feel pain during anesthesia? A critical review on surgery-evoked circulatory changes and pain perception

Cividjian et al. Best Pract & Res Clin Anaesh 2017



Les voies ascendantes et descendantes de la douleur font une boucle.

Neurostransmetteurs multiples: serotonine, noradrenaline, enkephalines, peptides

Il n'y a pas de raison pour que l'anti-nociception ne soit obtenue qu'en interférant avec les enképhalines via les opiacés.

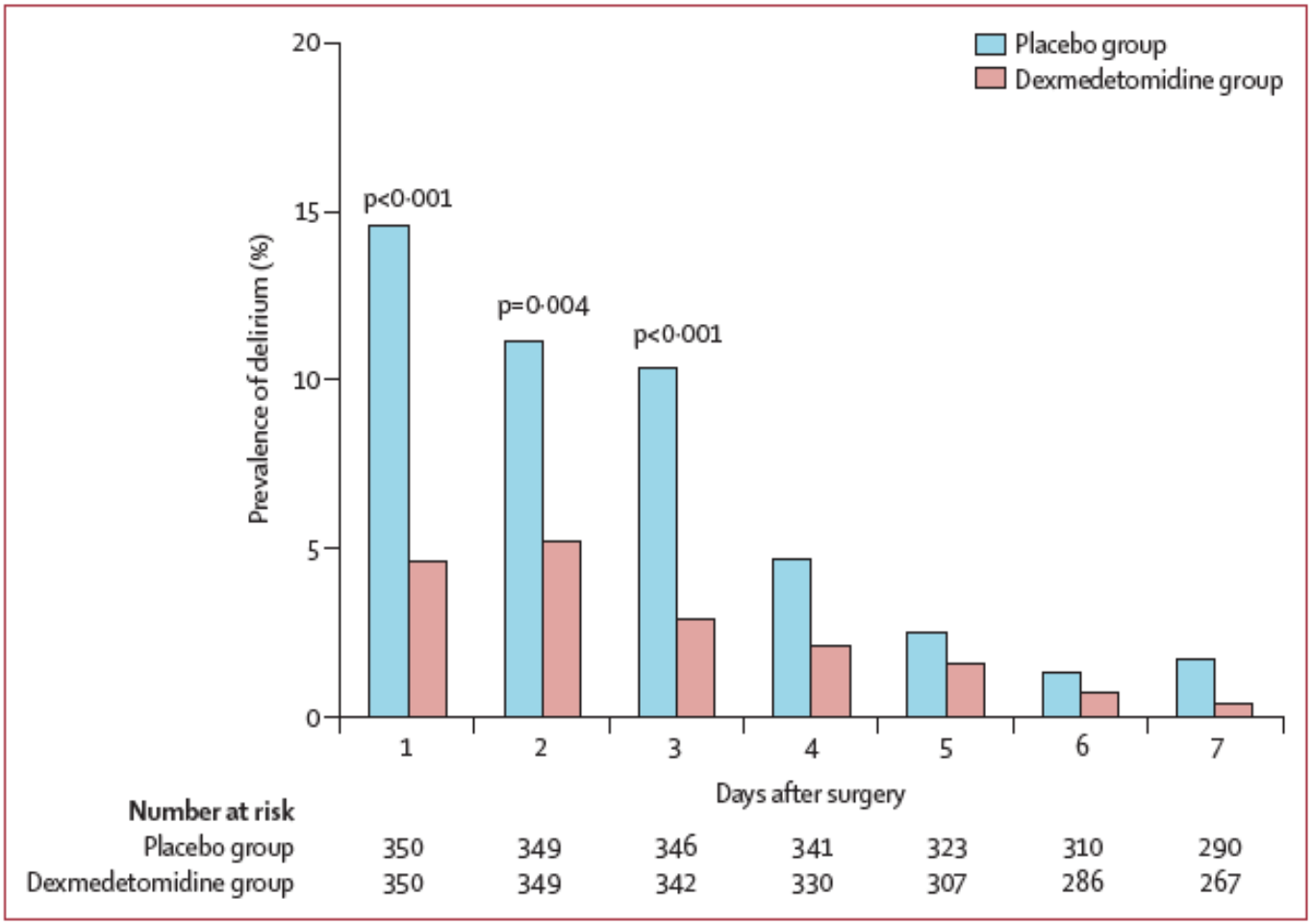
Il est possible d'obtenir de l'anti-nociception en interférant avec les autres neurotransmetteurs

Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial

Su et al, Lancet 2016

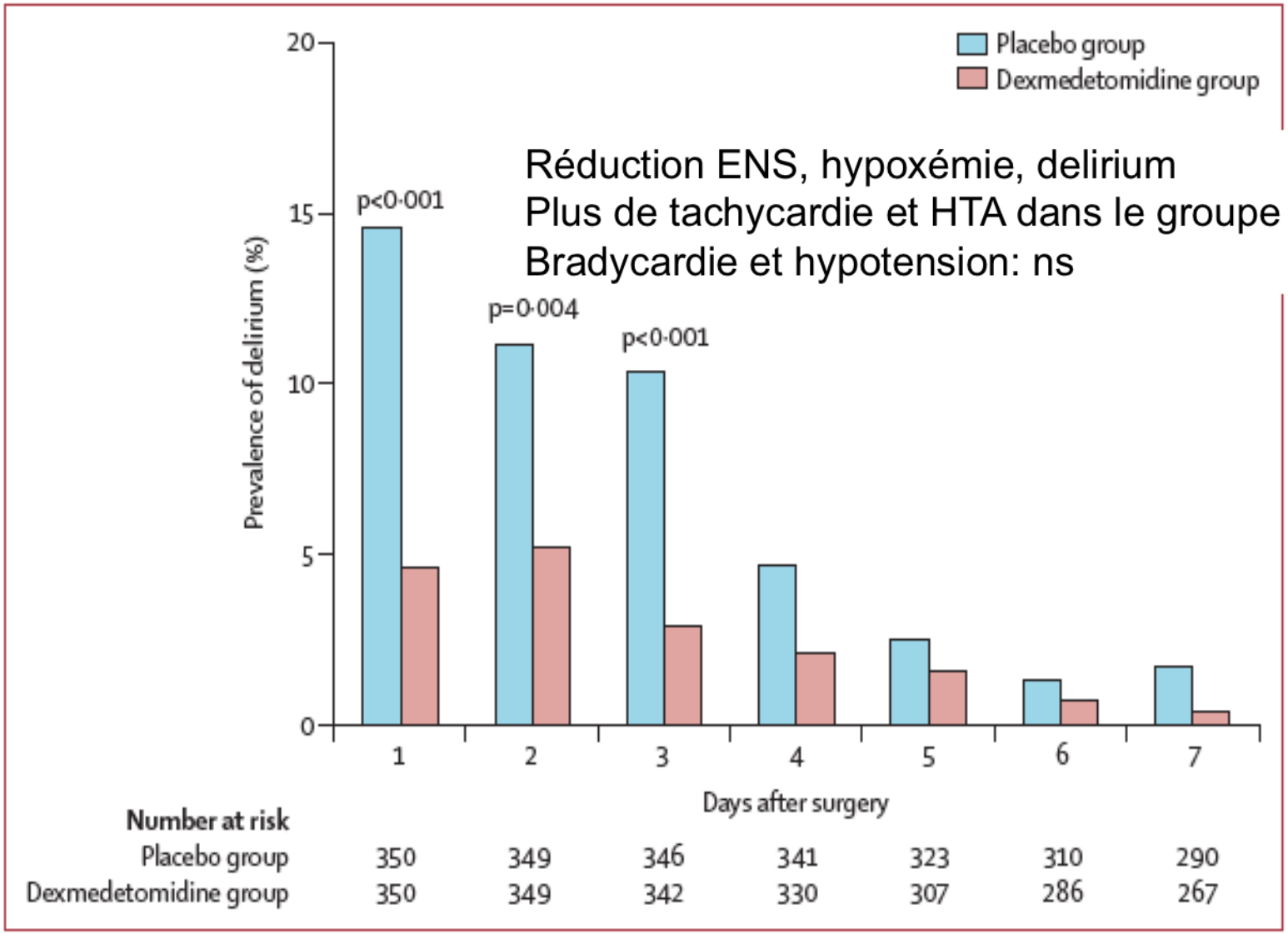
350 patients / groupe

Dex vs placébo en postop 12h, 0.1 microg/kg/h



Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial

Su et al, Lancet 2016



Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery A Randomized Clinical Trial

Deiner et al, Jama Surg 2017

404 patients (189 vs 201)

Dex vs placébo perop + 2h postop, 0.5 microg/kg/h

Table 4. Clinical Outcomes and Intraoperative Serious Events

Variable	Overall (N = 390)	Intervention (n = 189)	Placebo (n = 201)	*P* Value
Delirium, No. (%)				
Postoperative delirium	46 (11.8)	23 (12.2)	23 (11.4)	.94
PACU delirium	14 (3.6)	6 (3.2)	8 (4.0)	
Both	9 (2.3)	5 (2.6)	4 (2.0)	
None	321 (82.3)	155 (82.0)	166 (82.6)	
Intraoperative bradycardia, No. (%)				
Requiring treatment	55 (14.1)	35 (18.5)	20 (10.0)	.06
Requiring interruption of the drug	4 (1.0)	2 (1.1)	2 (1.0)	
Resolved spontaneously	87 (22.3)	45 (23.8)	42 (20.9)	
Did not occur	244 (62.6)	107 (56.6)	137 (68.2)	
Intraoperative hypotension, No. (%)				
Requiring treatment	150 (38.5)	81 (42.9)	69 (34.3)	.36
Requiring interruption of the drug	8 (2.1)	3 (1.6)	5 (2.5)	
Resolved spontaneously	39 (10.0)	18 (9.5)	21 (10.4)	
Did not occur	193 (49.5)	87 (46.0)	106 (52.7)	
Intraoperative hypertension, No. (%)				
Requiring treatment	62 (15.9)	26 (13.8)	36 (17.9)	.10
Requiring interruption of the drug	1 (0.3)	0	1 (0.5)	
Resolved spontaneously	47 (12.1)	17 (9.0)	30 (14.9)	
Did not occur	280 (71.8)	146 (77.2)	134 (66.7)	
Death, No. (%)	4 (1.0)	1 (0.5)	3 (1.5)	.35
Serious adverse event, No. (%)	22 (5.6)	13 (6.9)	9 (4.5)	.30
Length of stay, median (IQR), d	4.0 (3.0-6.0)	4.0 (3.0-6.0)	4.0 (3.0-6.0)	.27