Stratégies antihyperalgésiques périopératoires et Effets sur les douleurs chroniques postopératoires

Mise au point en 2015

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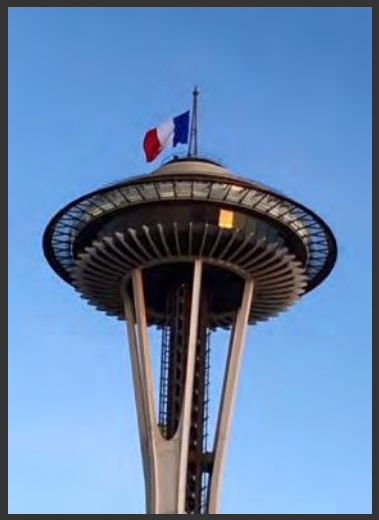
Université de Montréal

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Chukchi Sea
Beaufort Sea
Bering Sea
UNITED STATES
Baffin Bay
Davis Strait
Labrador Sea
CANADA
Hudson Bay
North
UNITED
STATES
Atlantic
Ocean
THE BAHAMAS
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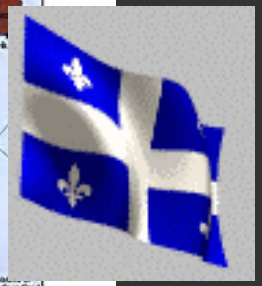
standard parallels 37°N and 65°N

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Moscow
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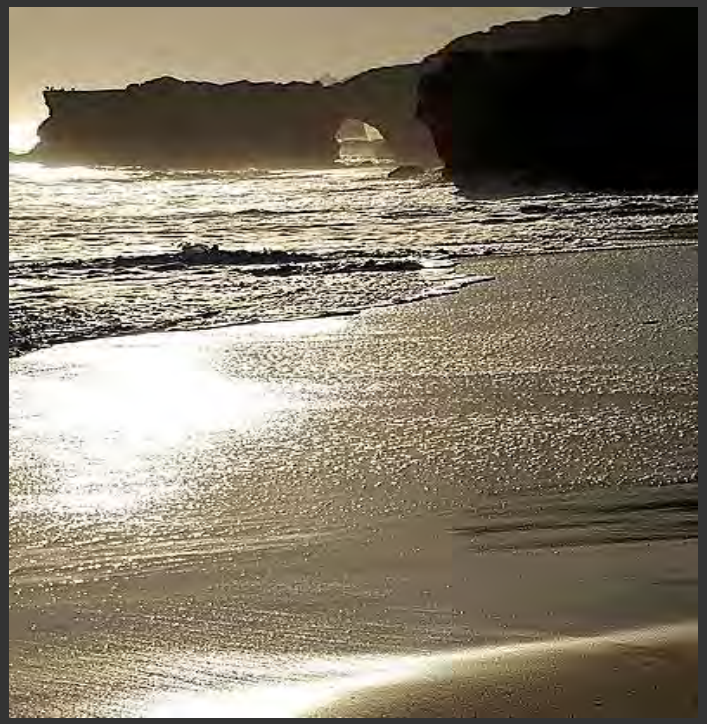
Lambert Conformal Conic Projection,
standard parallels 40°N and 56°N



Seattle : 2008-2014

Montreal : 2014-présent

Disclosures

- Grants from:
  - INSERM, France
  - Universite de Bordeaux, France
  - SFAR
  - SFETD
  - Compagnies Pharmaceutiques (Investigator Initiated Research Grants) en France, USA, Canada: Air Liquide, Biocodex, Cadence Pharmaceuticals, Pfizer, Medasense LTD
  - National Institute for Health research (NIH)
  - The Department of Anesthesiology at UWMC, Seattle
  - The University of Washington, Seattle
- I have no financial interest in any of the companies above mentioned

Definition PPSP

(PPSP = Persistent PostSurgical Pain)

Les PPSP ont été définies par la “International Association for the Study of Pain (IASP)” comme un disconfort clinique qui dure depuis plus de deux mois après chirurgie.

Incidence

Chronic Pain as an Outcome of Surgery

A Review of Predictive Factors

Anesthesiology 2000; 93:1123–33

Frederick M. Perkins, M.D., Henrik Kehlet, M.D., Ph.D.†*

Persistent postsurgical pain: risk factors and prevention

Henrik Kehlet, Troels S Jensen, Clifford J Woolf

Lancet 2006; 367: 1618–25

	Estimated incidence of chronic pain	Estimated chronic severe (disabling) pain (>5 out of score of 10)	US surgical volumes (1000s)†
Amputation[2]	30–50%	5–10%	159 (lower limb only)
Breast surgery (lumpectomy and mastectomy)[3]	20–30%	5–10%	479
Thoracotomy[4–7]	30–40%	10%	Unknown
Inguinal hernia repair[8–10]	10%	2–4%	609
Coronary artery bypass surgery[11–13]	30–50%	5–10%	598
Caesarean section[14]	10%	4%	220

- Schug et al., 2012: prévalence PPSP:
  - Reduction de 40% a 18% si on ne prend en compte que les douleurs de plus de 3/10 dans la zone de la chirurgie
  - Seulement 6% si on exclut tous les patients qui avaient déjà des douleurs chroniques dans la zone opérée avant la chirurgie

The neuropathic component in persistent postsurgical pain: A systematic literature review ☆

PAIN® 154 (2013) 95–102

Simon Haroutiunian [a,*], Lone Nikolajsen [a,b], Nanna Brix Finnerup [a], Troels Staehelin Jensen [a,c]

281 studies that investigated PPSP after 11 types of surgery. The prevalence of PPSP in each surgical group was examined. The prevalence of NeuP was determined by applying the recently published NeuP probability grading system. The prevalence of probable or definite NeuP was high in patients with persistent pain after thoracic and breast surgeries—66% and 68%, respectively. In patients with PPSP after groin hernia repair, the prevalence of NeuP was 31%, and after total hip or knee arthroplasty it was 6%.

Neuropathic Aspects of Persistent Postsurgical Pain: A French Multicenter Survey With a 6-Month Prospective Follow-Up

Christian Dualé, *,†,‡ Lemlih Ouchchane, §,||,¶ Pierre Schoeffler, ‡,§,** the EDONIS Investigating Group [1], and Claude Dubray *,†,‡,§

The Journal of Pain, Vol 15, No 1 (January), 2014

at the third and sixth months after surgery. In the 2,397 patients who completed follow-up, the cumulative risk of N-PSPP within the 6 months ranged from 3.2% (laparoscopic herniorrhaphy) to 37.1% (breast cancer surgery).

Facteurs de Risque
et
Spécificités de Populations

Facteurs de Risque

- Les facteurs de risque classiques :
  - Douleur préopératoire
  - Consommation d'analgésique préopératoire importante,
  - Et haut niveaux de douleur postopératoire

- Corrélation entre PPSP et le degré préopératoire de :
  - "Catastrophizing" (tendance a exagerer le pessimisme sur le devenir),
  - Anxiété,
  - Peur de la chirurgie et de la Douleur PostOp (DPO),
  - Absence de support dans l'environnement du patient,
  - Et/ou réponse exagérée au stimuli expérimentaux (quantitative sensory testing: QSTs)

Facteurs de Risque

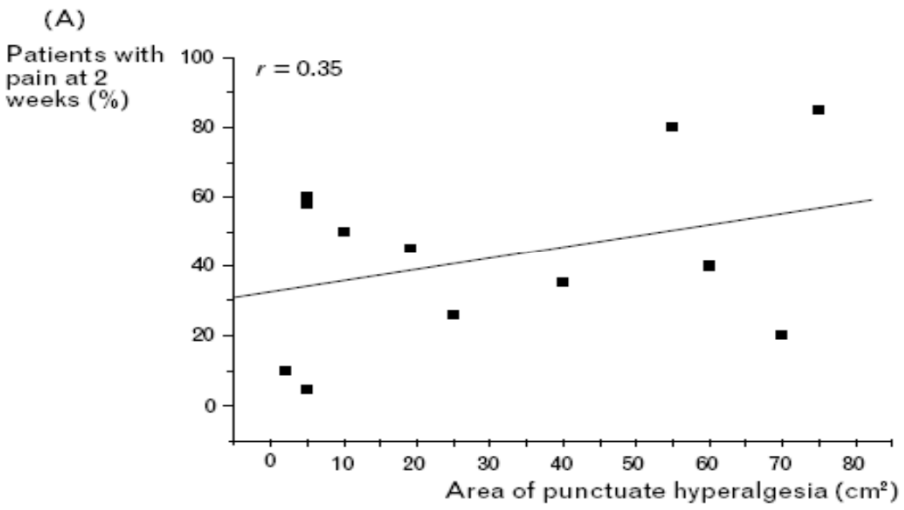
- Variations dues à la génétique :
  - COMT (catecholamine-O-methyl-transferase) polymorphisme : est associé avec des variations de sensibilité à la douleur
  - melanocortin-1 receptor gene polymorphisme : chez les femmes rousses, est associé à une plus haute réponse à certains opioïdes
  - Cependant aucun “single nucleotide polymorphism” (SNP) n’a été réellement corrélé avec le risque de développer des PPSP

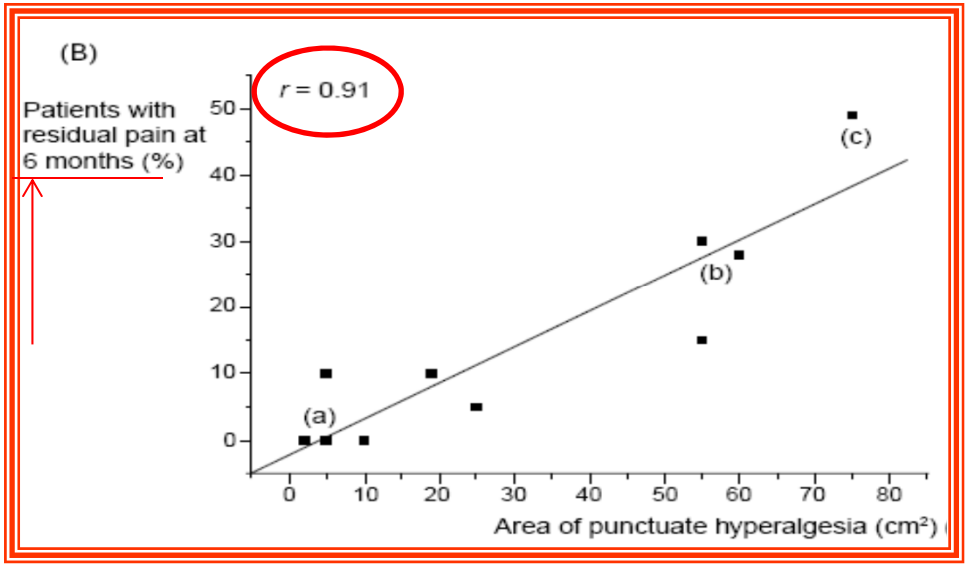
Correlation entre

Hyperalgésies Précoces

et

PPSP





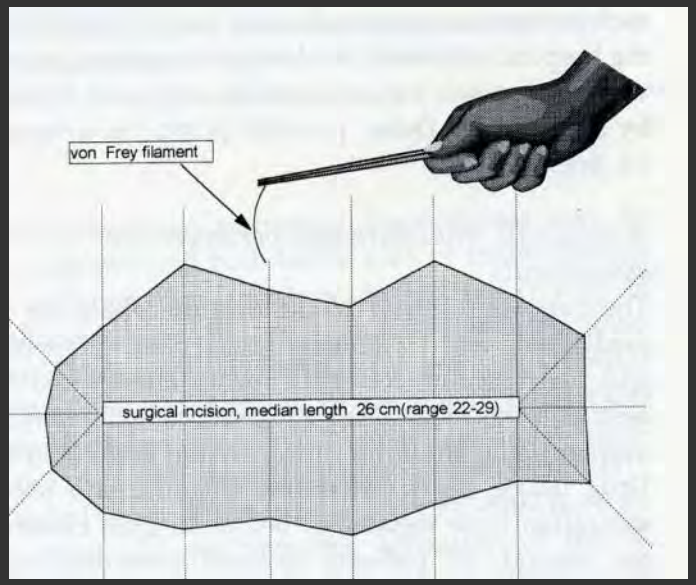
Lavand'homme P, Current opinion in Anesthesiology 2006
Eisenach J, RAPM 2006

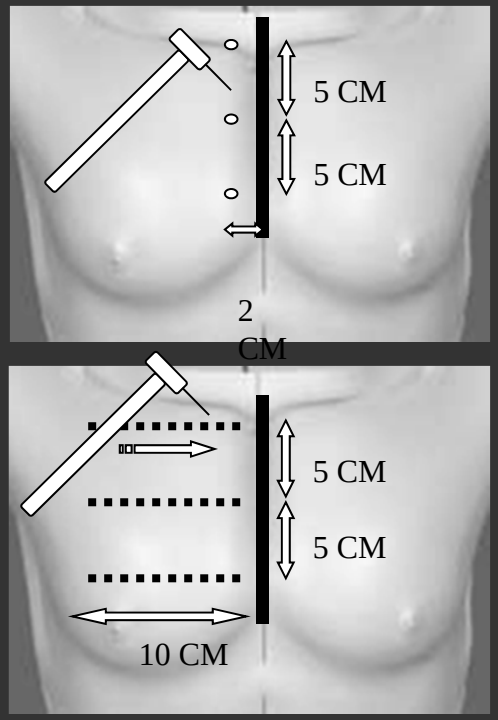
“Hyperalgésie”

Acta Anaesthesiol Scand. 1997 Oct;41(9):1124-32.

Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery.

Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A.

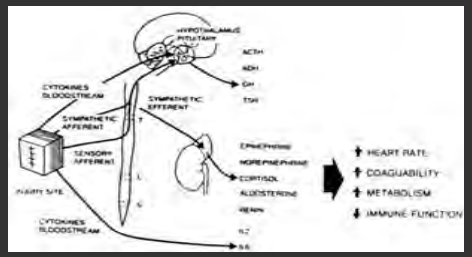




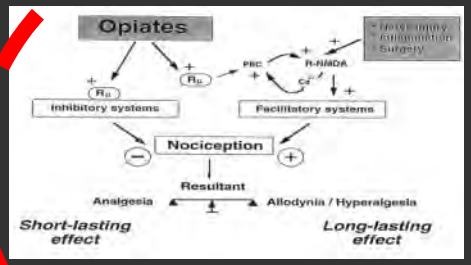
Pathophysiologie du développement des PPSP

- trauma chirurgical
- absence d'analgésie multimodale

A- Influx nociceptifs



Sensibilisation périphérique et centrale _ lésion nerveuse

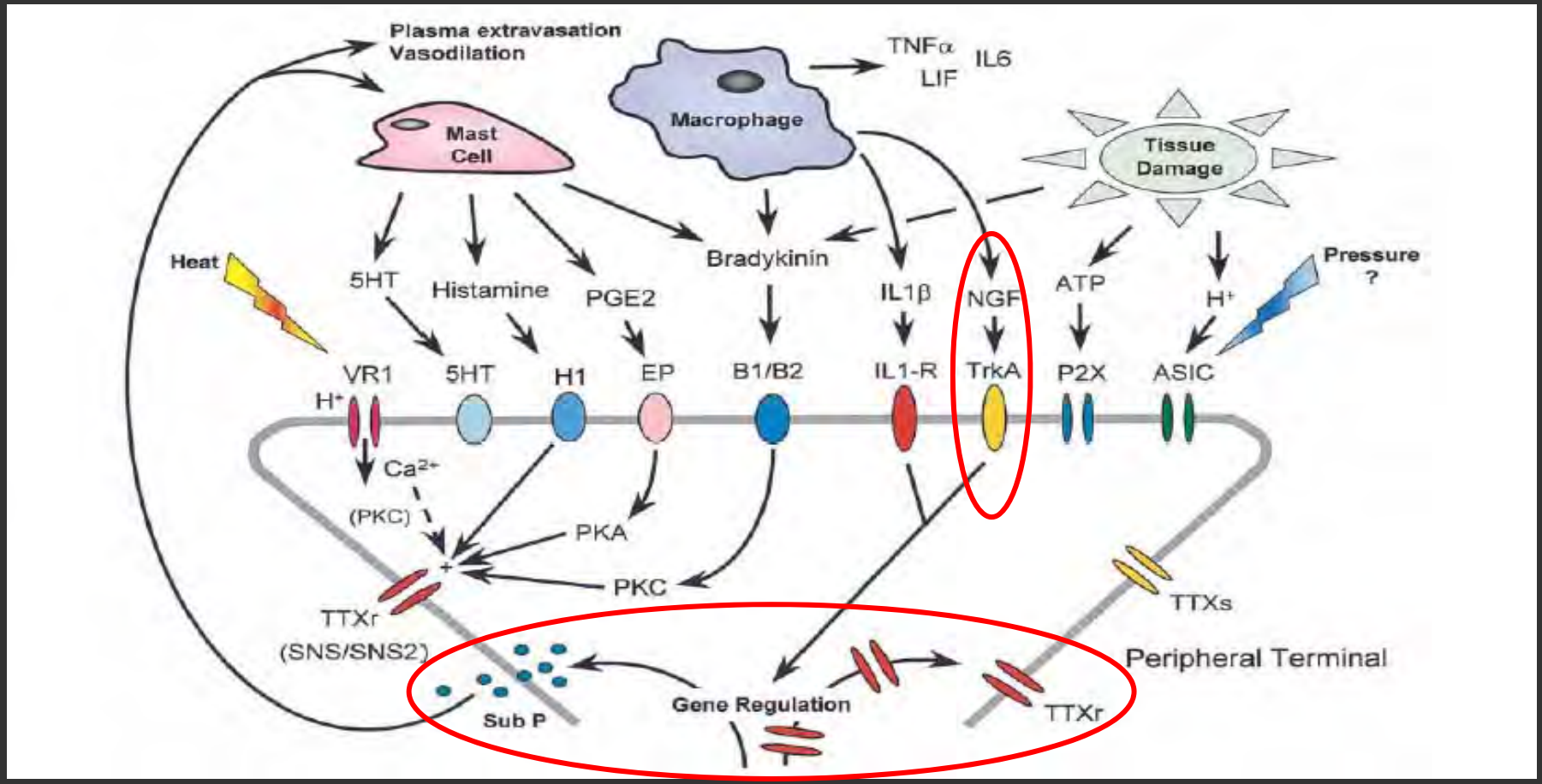


B- Opioides

« PPSP »

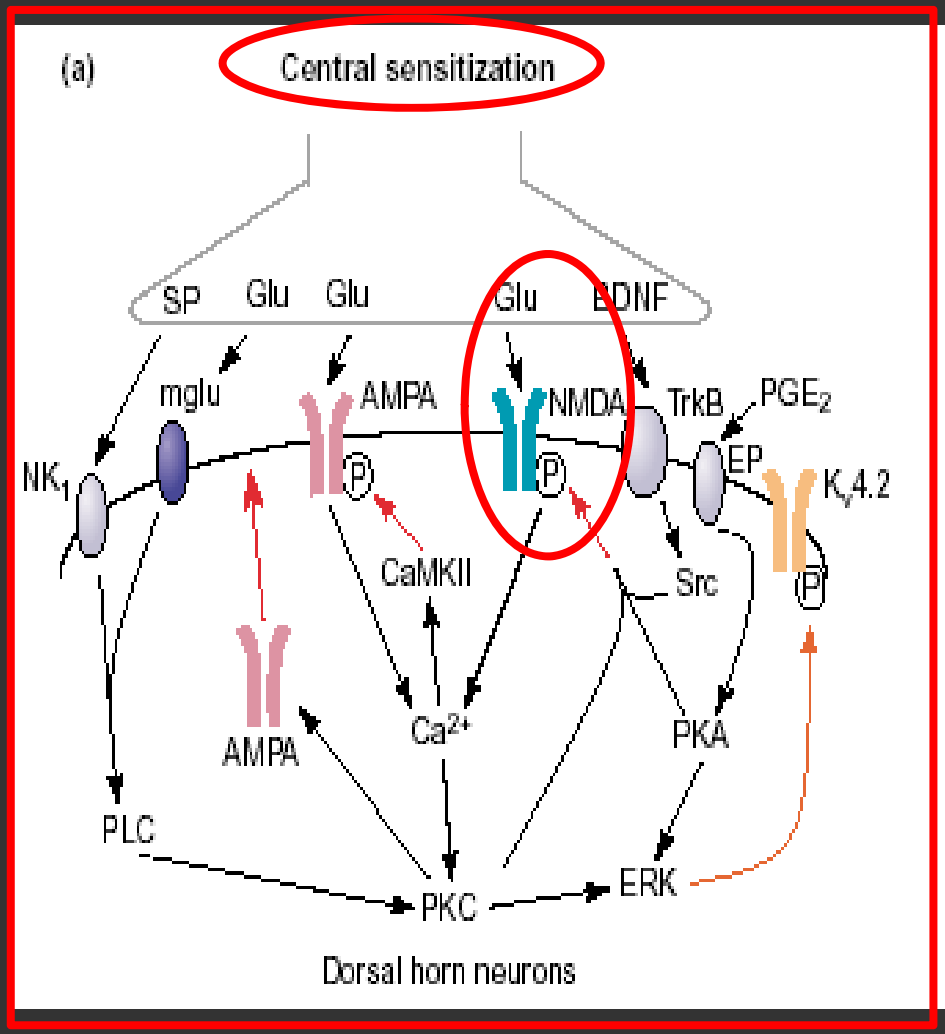
- hautes doses d'opioïdes intraopératoires
- absence de stratégies anti-sensibilisantes

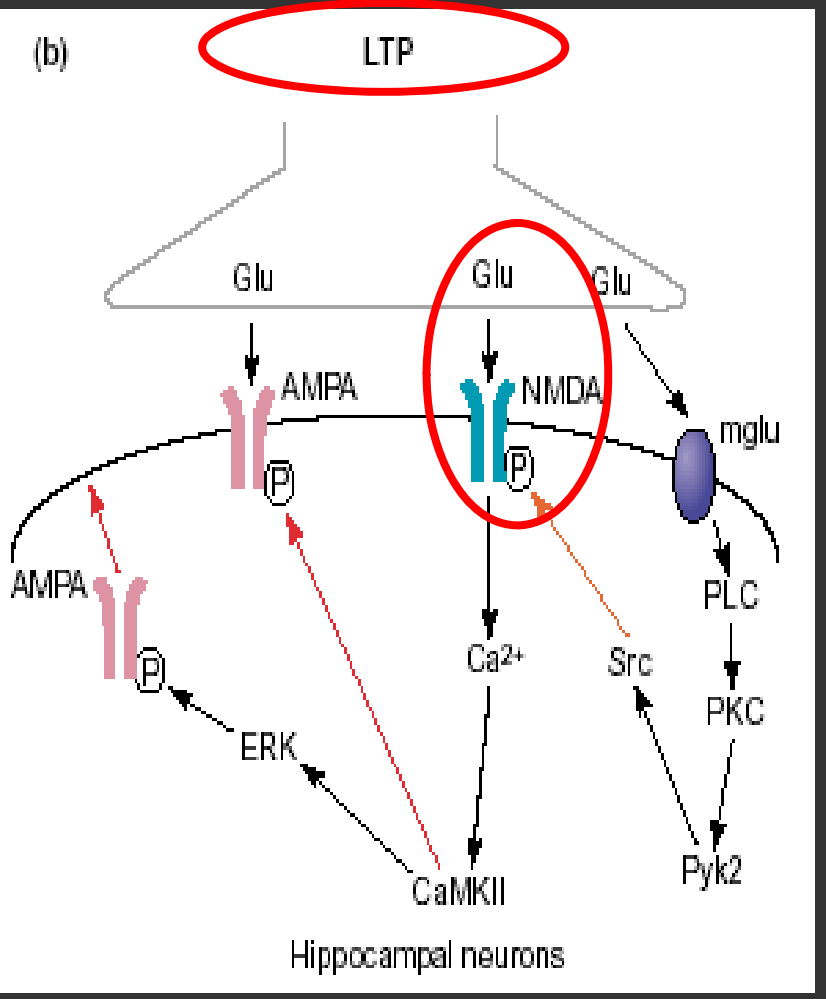
Sensibilisation périphérique



Costigan M. and Woolf C.J. The Journal of Pain, 2000

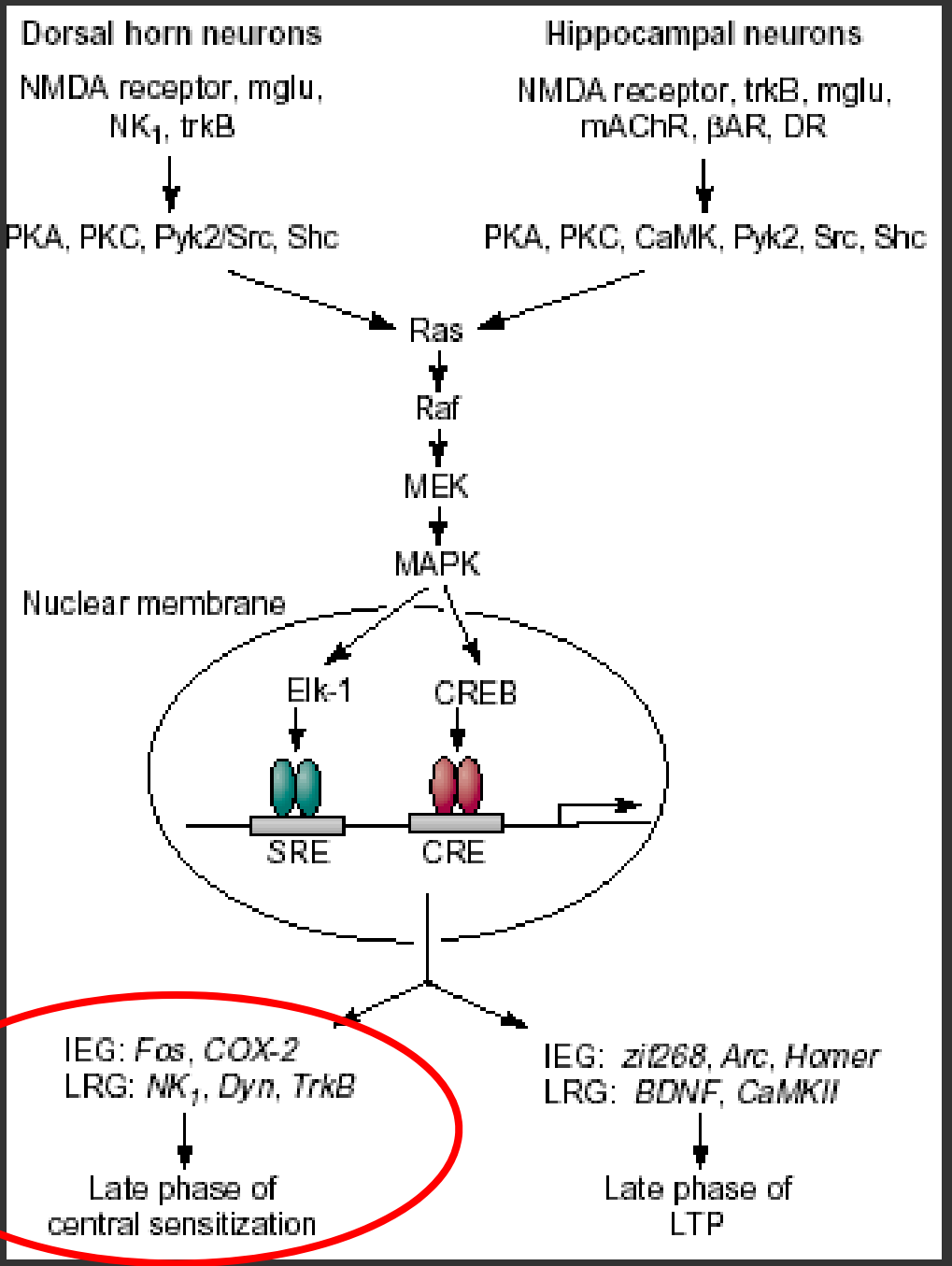
Sensibilisation centrale



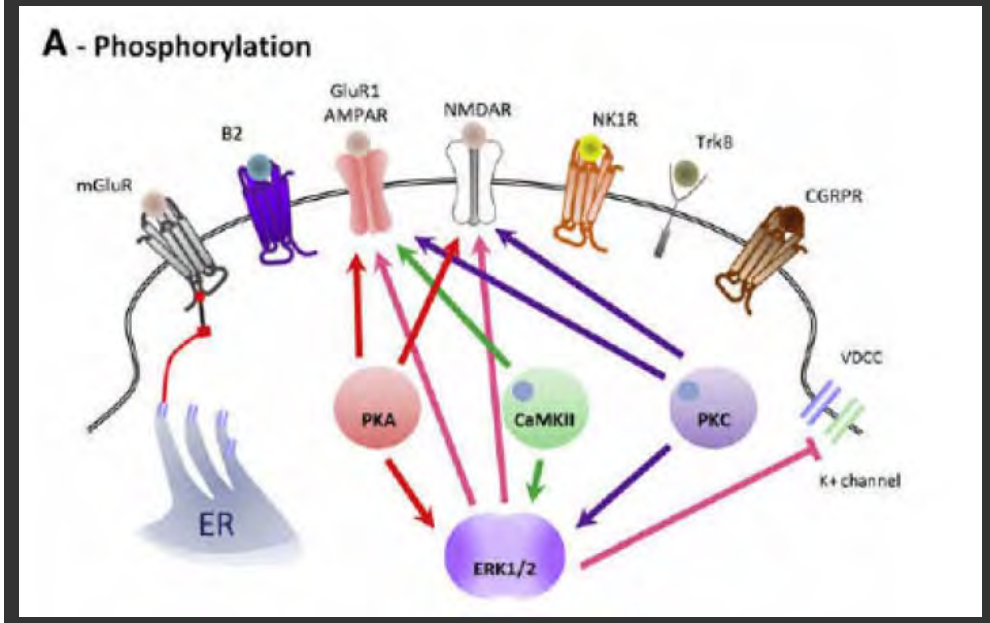


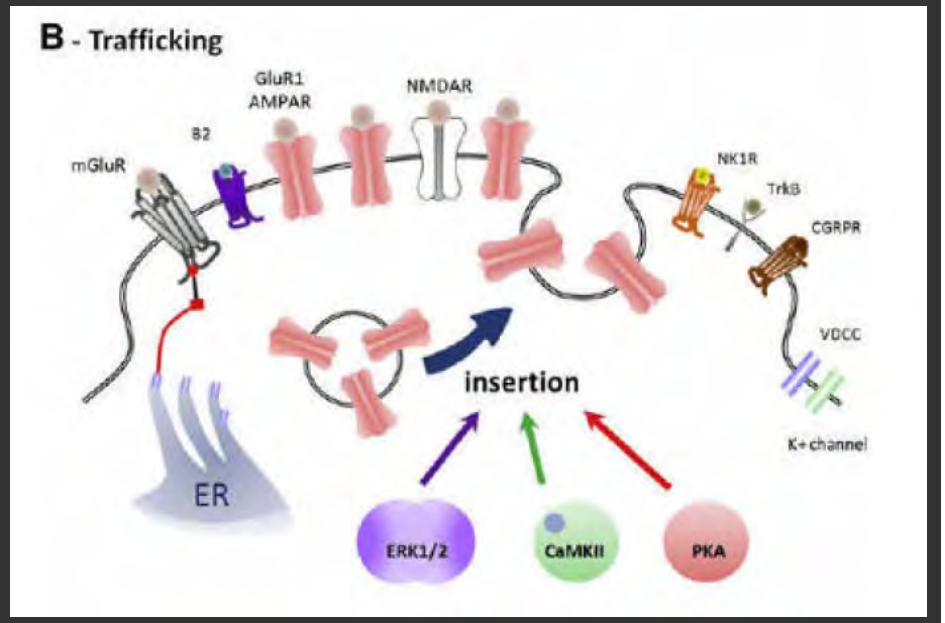
Ji RR et al, Trends in Neurosciences 2003

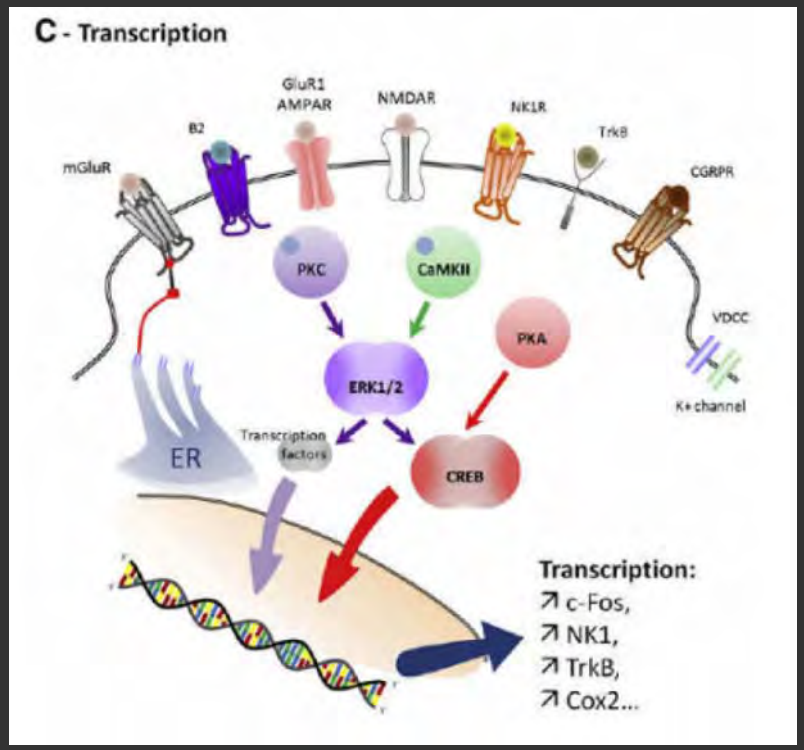
Sensibilisation centrale



Ji RR et al, Trends in Neurosciences 2003







Latremoliere and Woolf J Pain 2009

Récepteurs NMDA

Krystal et al, Pharmacol. Ther., 2003

Opioid Induced Hyperalgesia OIH

Saline or Fentanyl
+
Incision

Saline group
Fentanyl group (4x100 µg/kg)

Paw pressure (g)

600
500
400
300
200
100
0

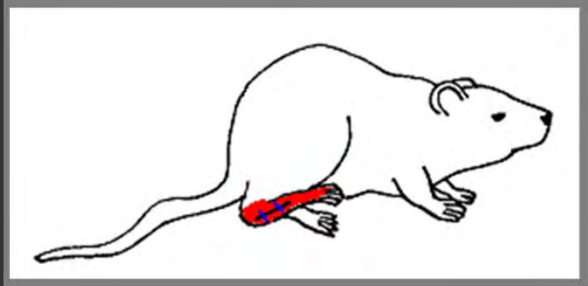
D_{-2} D_0 D_{+1} D_{+3} D_{+5} D_{+7}

0 2 4 6
Hours

Time

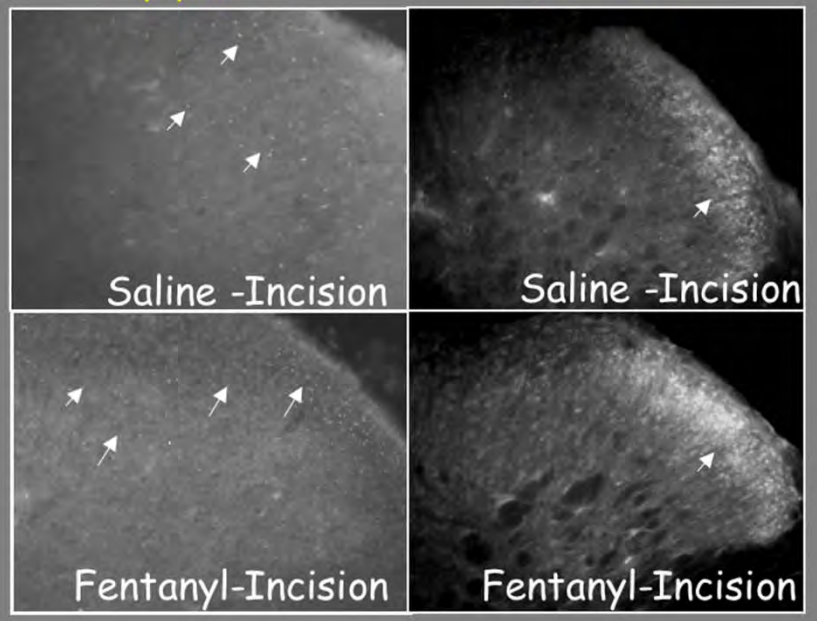
Richebé et al. Anesthesiology (2005) 102 (2) 421-428

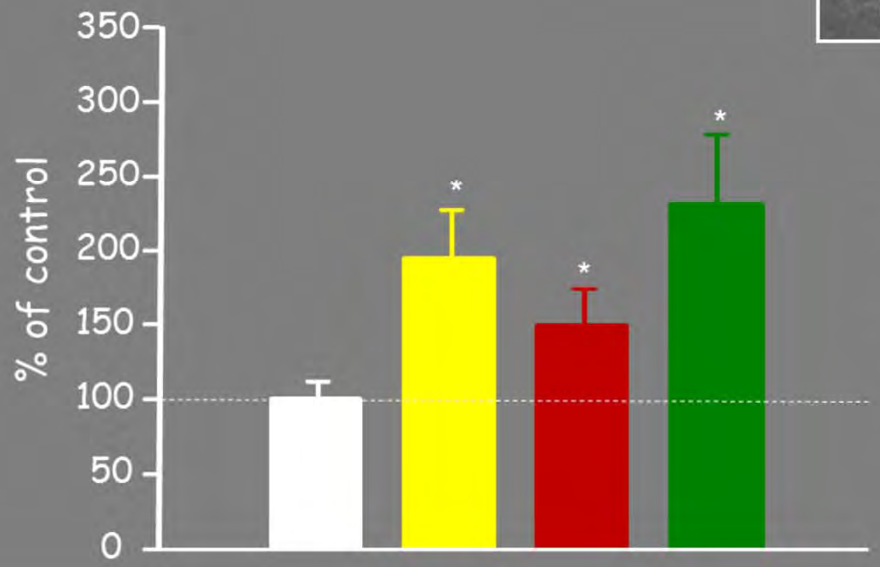
Opioid Induced Hyperalgesia

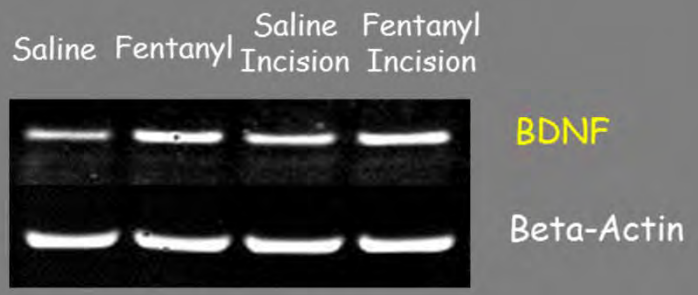


No Fentanyl

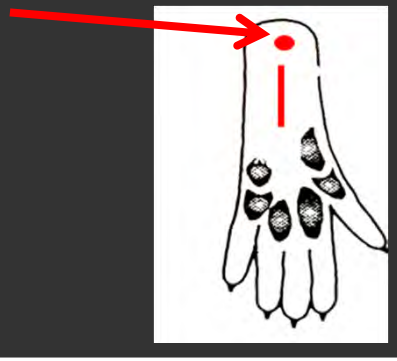
Fentanyl





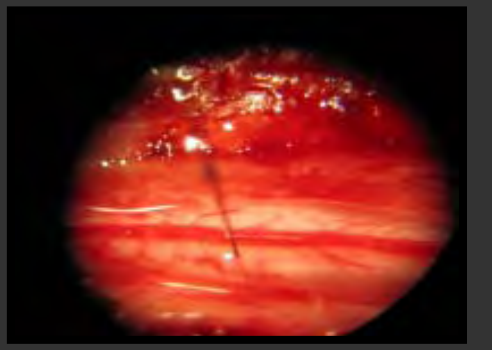


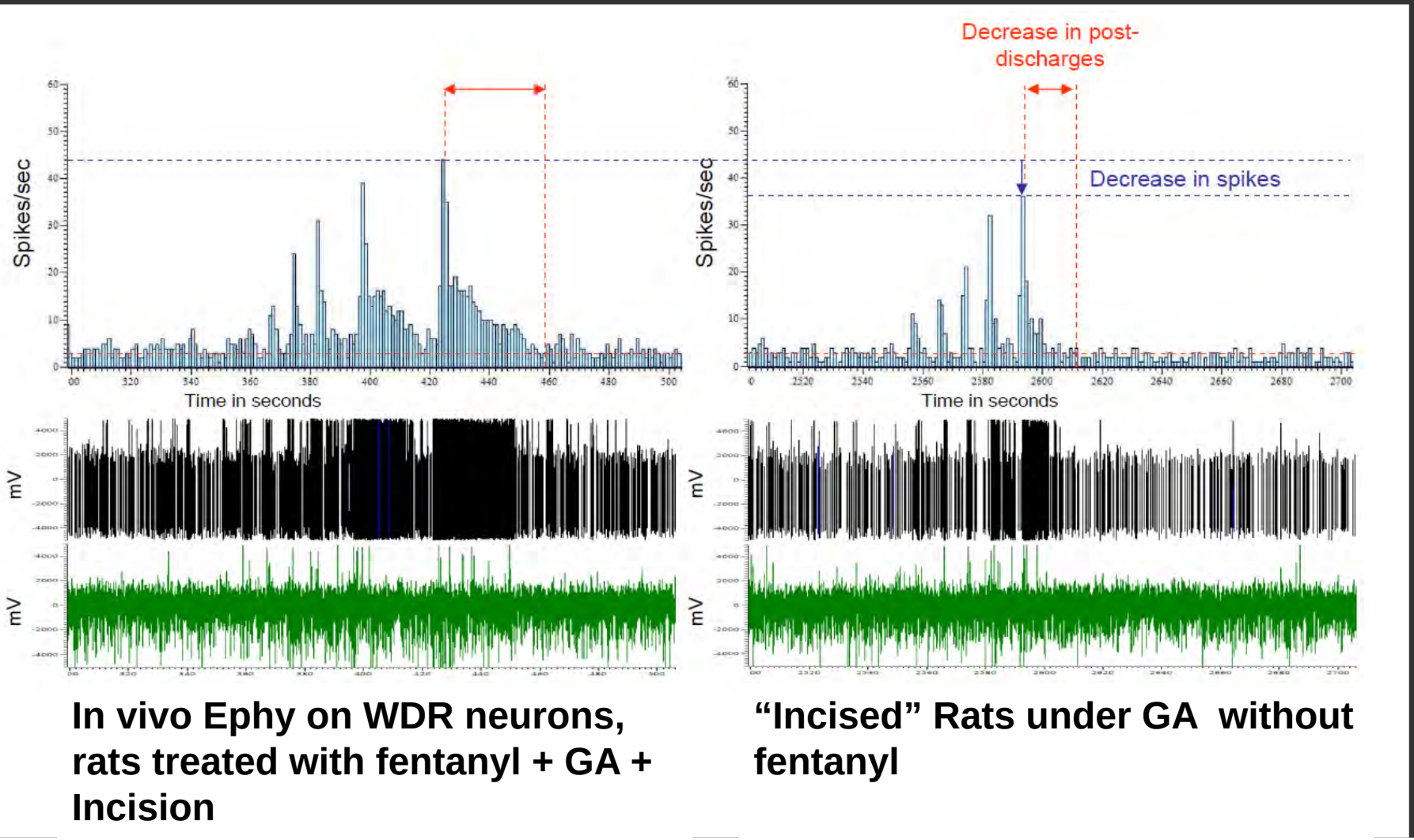
Rivat, Richebe, in progress



Richebe et al. 2012

Opioid Induced Hyperalgesia





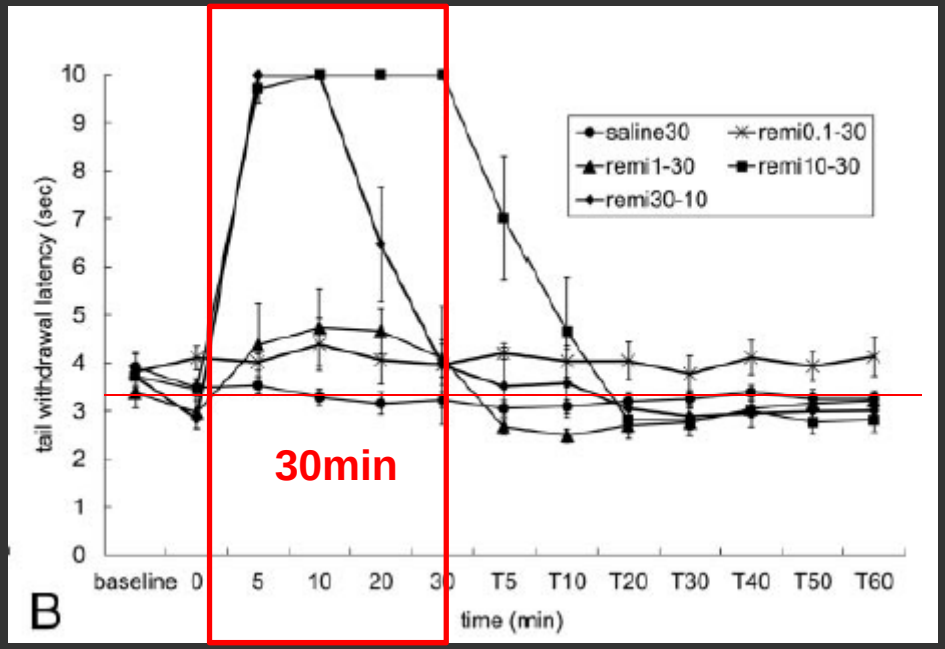
In vivo Ephy on WDR neurons, rats treated with fentanyl + GA + Incision

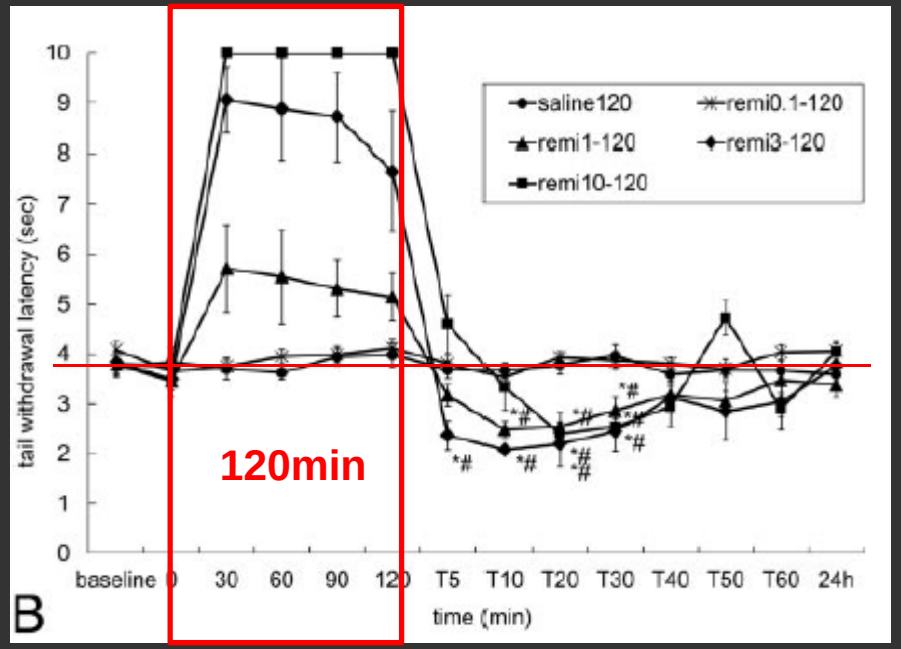
“Incised” Rats under GA without fentanyl

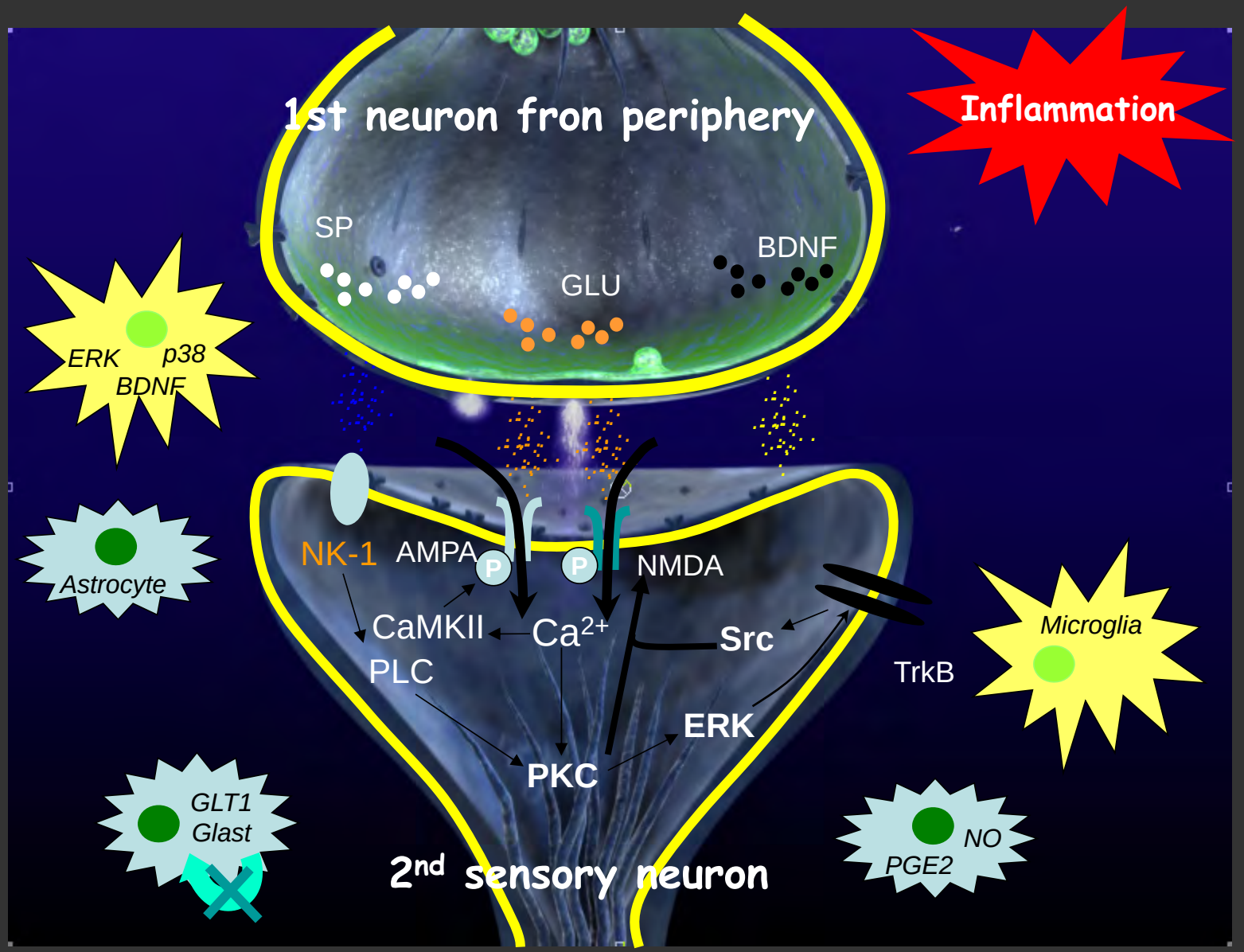
Intravenous Infusion of Remifentanil Induces Transient Withdrawal Hyperalgesia Depending on Administration Duration in Rats

Ryosuke Ishida, MD,* Tetsuro Nikai, MD,* Tatsuya Hashimoto, MD, PhD,* Toshiko Tsumori, PhD,† and Yoji Saito, MD, PhD*

(Anesth Analg 2012;114:224–9)






1st neuron fron periphery
Inflammation
SP
GLU
BDNF
ERK
p38
BDNF
Astrocyte
NK-1
AMPA
P
P
NMDA
CaMKII
Ca2+
PLC
Src
TrkB
Microglia
ERK
PKC
GLT1
Glast
NO
PGE2
2nd sensory neuron

Approche pratique en Anesthésie

Opioid-Induced Hyperalgesia (OIH)

chez l'homme?

Premières études…

Intraoperative high dose fentanyl induces postoperative fentanyl tolerance

- **Induction: 1 versus 15mcg/kg IV fentanyl**
- **Maintenance: 0 versus 100mcg/h**

CANADIAN JOURNAL OF ANESTHESIA

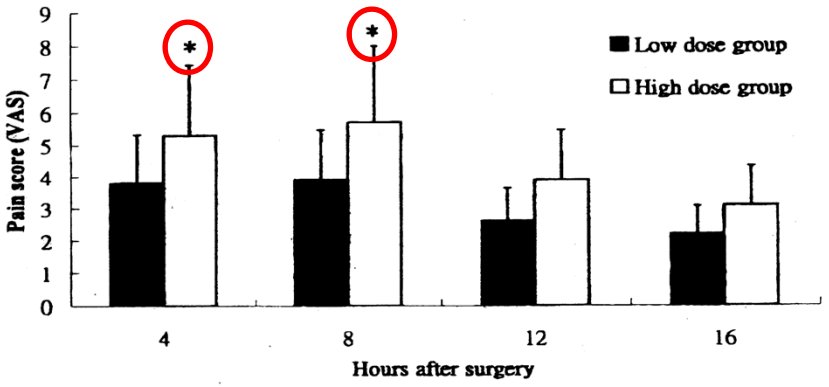


FIGURE 1 Postoperative visual analogue scores (VAS) (mean ± SD) during the first postoperative 16 hr. *: $P < 0.05$.

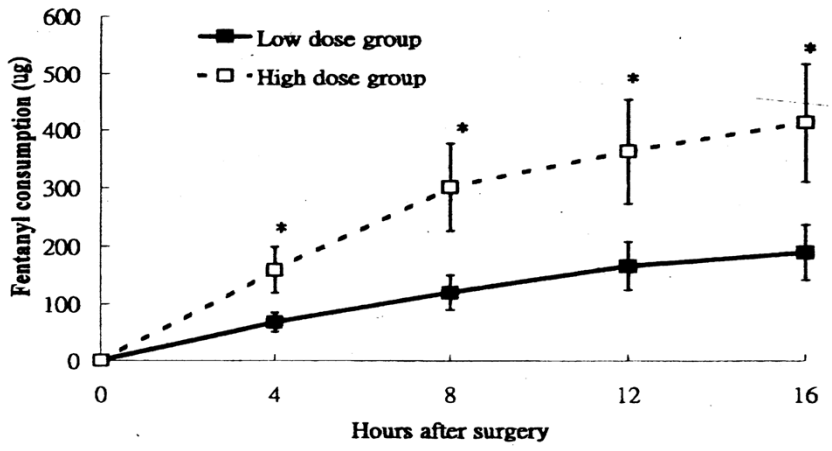


FIGURE 2 Postoperative accumulated fentanyl consumption (μg) (mean ± SD) during the first 16 hours after surgery. *: $P < 0.05$.

Chia Y.Y. et al, CJA 1999

Anesthesiology 2005; 103:147–55

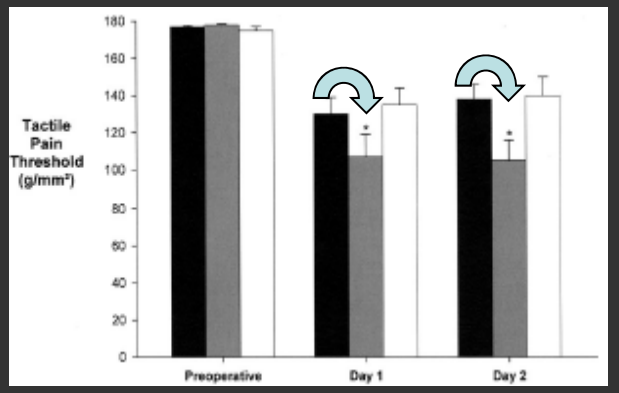
Remifentanil-induced Postoperative Hyperalgesia and Its Prevention with Small-dose Ketamine

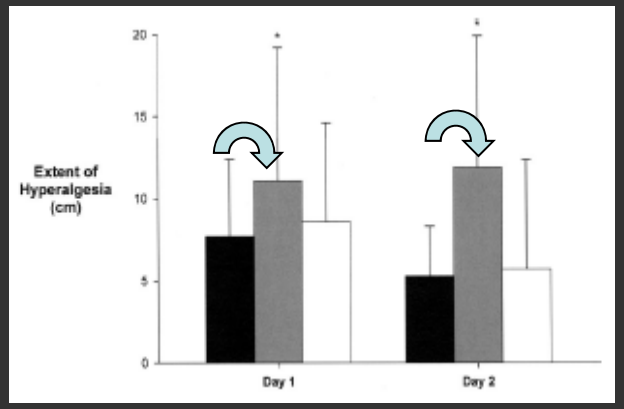
Vincent Joly, M.D., Philippe Richebe, M.D.,† Bruno Guignard, M.D.,* Dominique Fletcher, M.D.,‡ Pierre Maurette, M.D.,§ Daniel I. Sessler, M.D.,‖ Marcel Chauvin, M.D.#*

	Small-dose Remifentanil (n = 25)	Large-dose Remifentanil (n = 25)	Large-dose Remifentanil–Ketamine (n = 24)
Remifentanil dose, mg	0.9 ± 0.3*	6.7 ± 3.1	6.5 ± 3.4
Desflurane, MAC/h	0.8 ± 0.2*	0.5 ± 0.2	0.6 ± 0.2
Ephedrine, No. of doses/No. of patients	9/17	10/13	50/15†
Final intraoperative temperature, °C	36.6 ± 0.7	36.3 ± 0.8	36.3 ± 0.9
Awakening time, min	14 ± 6	13 ± 5	14 ± 6
Extubation time, min	16 ± 6	14 ± 6	15 ± 4
Time to first postoperative morphine, min	35 (28–46)	24 (20–33)	41 (32–52)
Morphine given in PACU, mg	16 (10–24)	20 (17–27)	20 (14–23)
0–48 h cumulative postoperative morphine consumption, mg	68 (50–91)	86 (59–109)‡	62 (48–87)
Postoperative nausea and vomiting, No. of patients	7	8	8
Droperidol, No. of doses/No. of patients	8/7	8/8	8/8

Remifentanil
0.05 mcg/kg/min
vs
0.4 mcg/kg/min

Abaissement seuil nociceptif





Augmentation des aires d'hyperalgésie

Joly, Richebé et al, Anesthesiology 2005

Lien entre doses d'opioïdes intraop. et PPSP

Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy

120 patients, thoracotomies, evaluation précoce et à 1 un

Table 5 Association between the intraoperative total dose of remifentanil and the remifentanil dose corrected for LBM and duration of surgery, and OR for chronic thoracic pain 1 yr after cardiac surgery. LBM, lean body mass

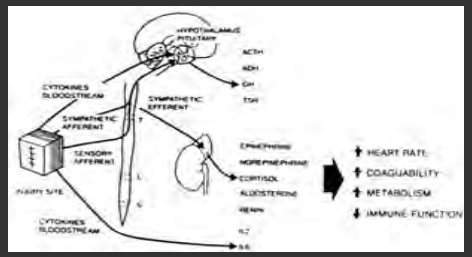
	No chronic pain ($n=72$)	Chronic pain ($n=18$)	Odds ratio	95% CI	*P*-value	*P*-value for trend
Total dose of remifentanil during surgery (mg) [*n* (%)]						
0	35 (49)	3 (17)	1		0.04	0.01
>0 and <1.7	19 (26)	6 (33)	3.68	0.8–16.4		
≥1.7	18 (25)	9 (50)	5.83	1.4–24.3		
Remifentanil [μg (kg LBM)$^{-1}$ (minute of surgery)$^{-1}$] [*n* (%)]						
0	35 (49)	3 (17)	1		0.02	0.005
>0 and <0.12	19 (26)	5 (28)	3.07	0.7–14.3		
≥0.12	18 (25)	10 (55)	6.48	1.6–26.5		

L. van Gulik et al, BJA 2012

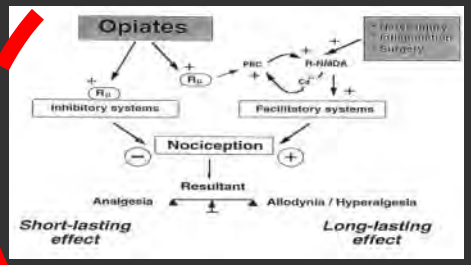
Solutions pratiques quotidiennes

- trauma chirurgical
- absence d'analgésie multimodale

A- Influx nociceptifs



Sensibilisation périphérique et centrale _ lésion nerveuse



B- Opioides

« PPSP »

- hautes doses d'opioïdes intraopératoires
- absence de stratégies anti-sensibilisantes

1/ Anesthésie Régionale

a) pour limiter les opioïdes intraop.

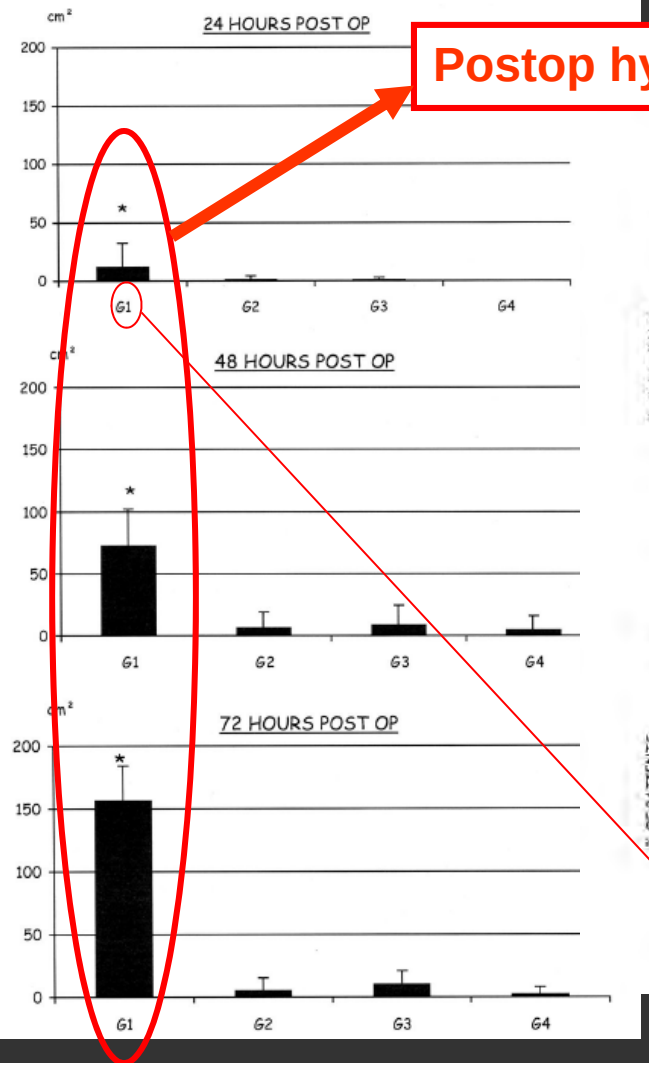
b) pour bloquer la sensibilisation à la douleur

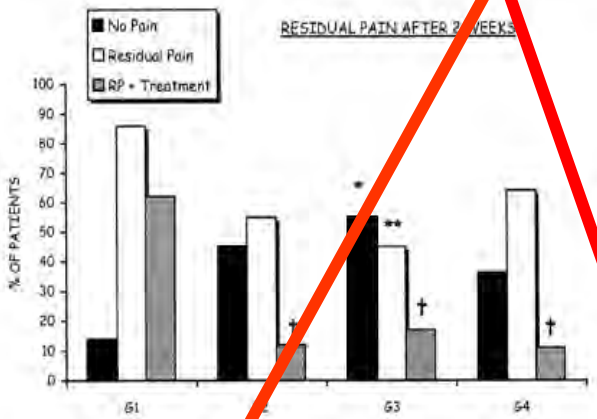
Anesthesiology 2005; 103:813–20

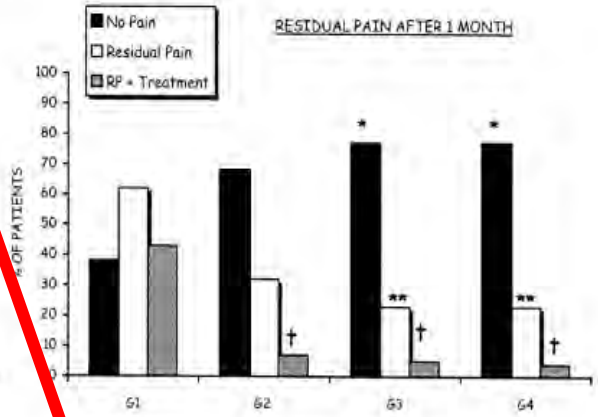
Intraoperative Epidural Analgesia Combined with Ketamine Provides Effective Preventive Analgesia in Patients Undergoing Major Digestive Surgery

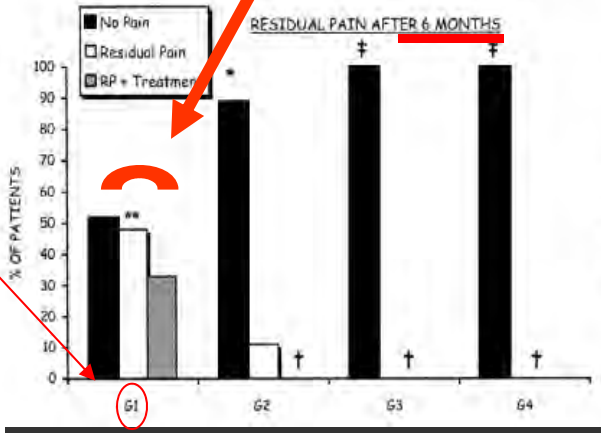
Patricia Lavand'homme, M.D., Ph.D., Marc De Kock, M.D., Ph.D.,† Hilde Waterloos, R.N.‡*

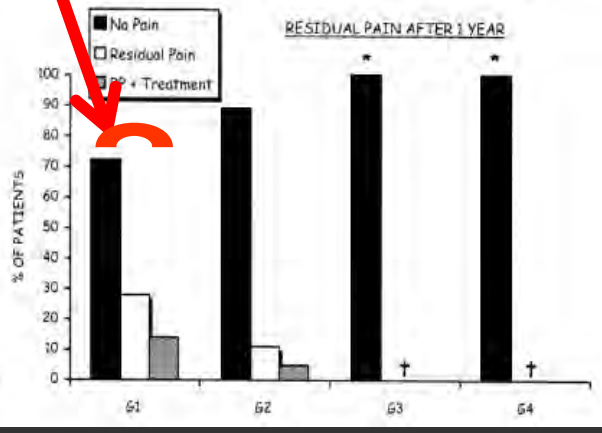
Postop hyperalgesia = Postop CHRONIC PAIN







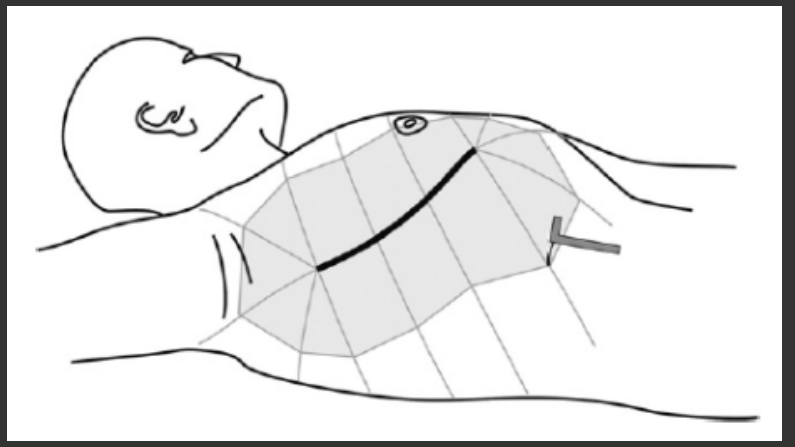


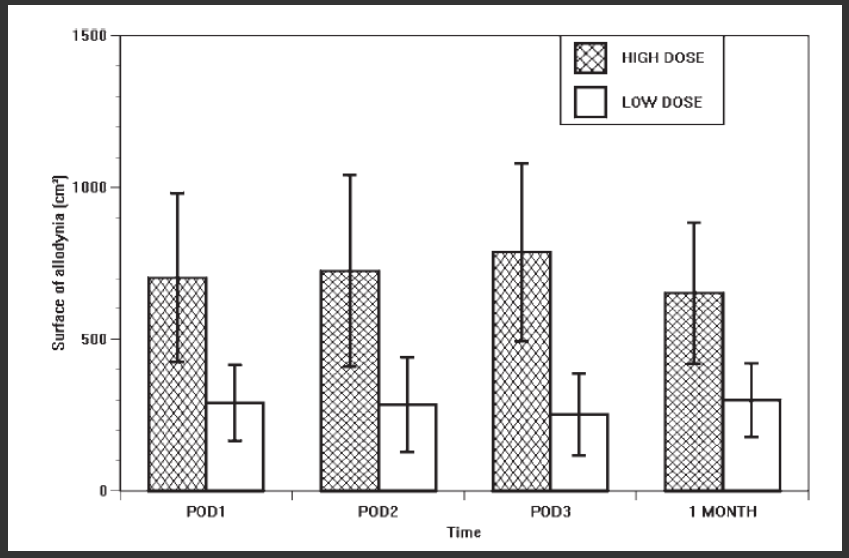


Different Anesthetic Techniques Associated with Different Incidences of Chronic Post-thoracotomy Pain: Low-Dose Remifentanil Plus Presurgical Epidural Analgesia is Preferable to High-Dose Remifentanil with Postsurgical Epidural Analgesia

Brussels, Belgium.

Interventions: High-dose remifentanil (average effect-site concentration 5.61 ± 0.84 ng/mL) with epidural analgesia started and at the end of surgery or low-dose remifentanil (average effect site concentration 1.99 ± 0.02 ng/mL) with epidural analgesia with 0.5% ropivacaine started at the beginning of anesthesia.





	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 JC et al, JCVA 2010

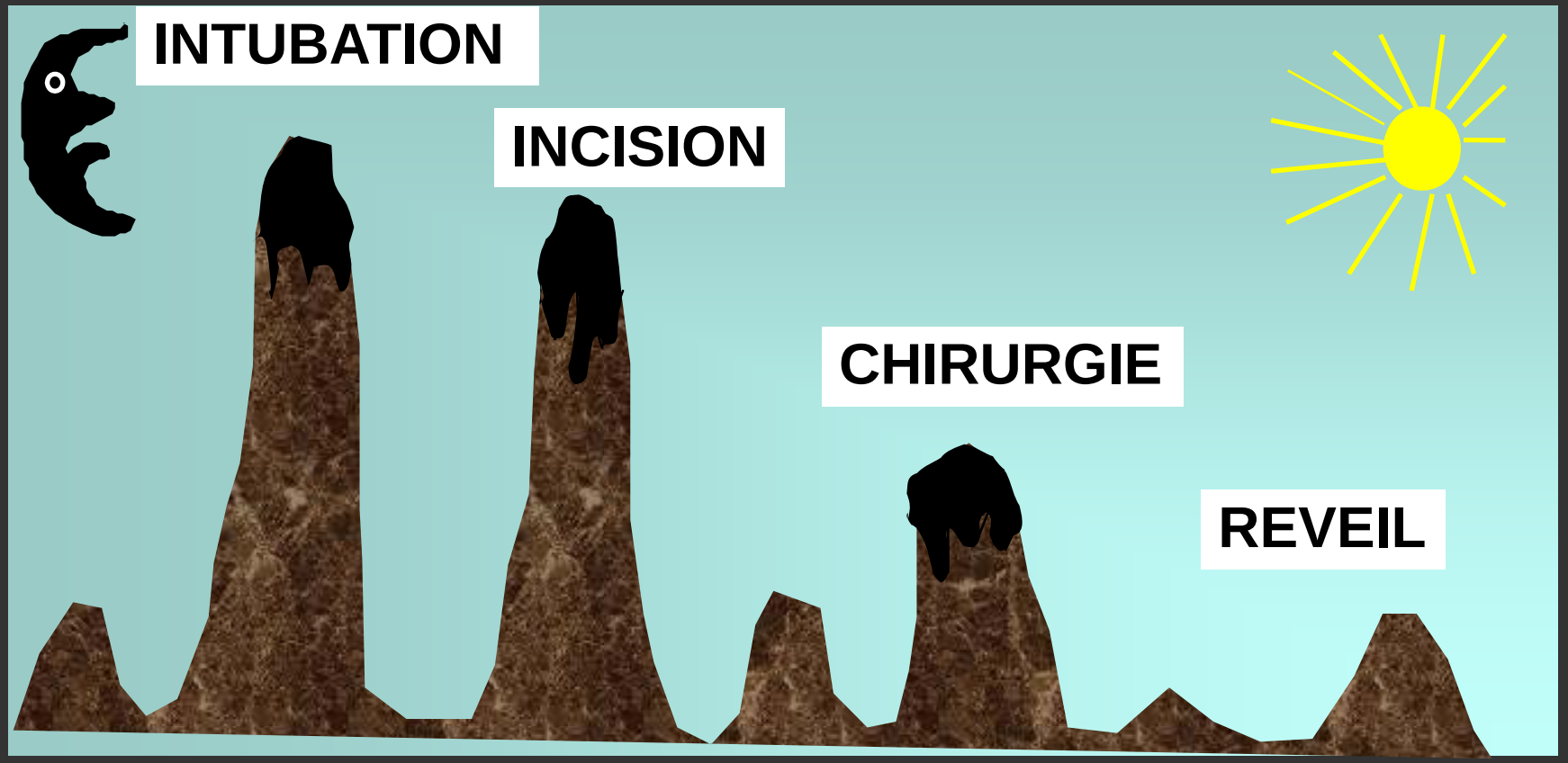
De plus,
Liu SS et al., Int Orthop 2012 (acute pain)
And Liu SS et al., RAPM 2012 (chronic pain)

- 1) AG versus bloc neuraxial central = facteur de risque pour plus de douleurs aigues après chirurgie de hanche et genoux :
  - OR 8.5 pour douleur au repos
  - OR 9.0 pour douleur durant l'activite

- 2) AG augmente le risque de PPSP à un an de la chirurgie : OR of 2.5

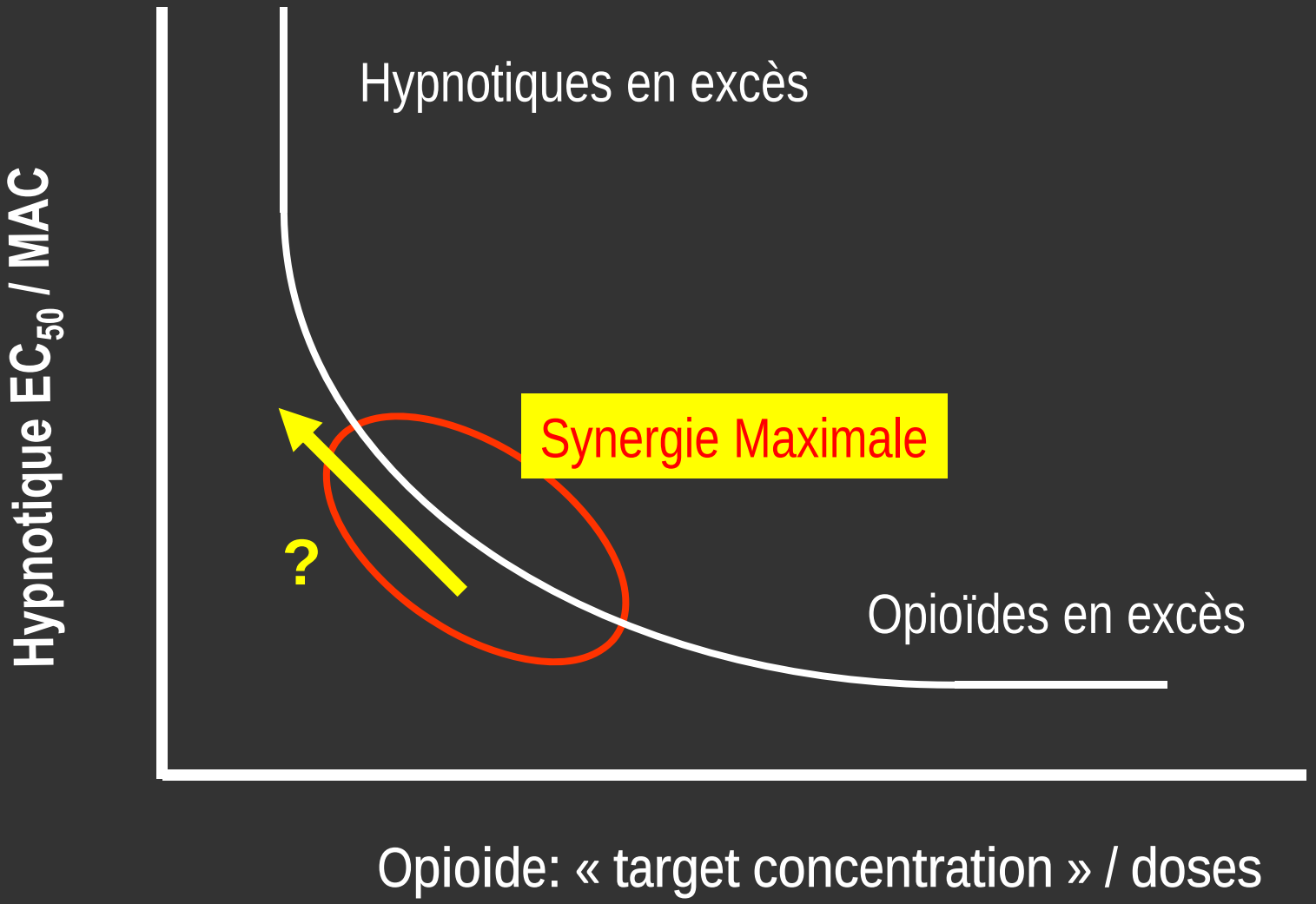
2/ Donner moins d'opioïdes intraop.

Variations des stimuli durant anesthésie…



(from GLASS et coll.)

Interaction opioïdes et hypnotiques

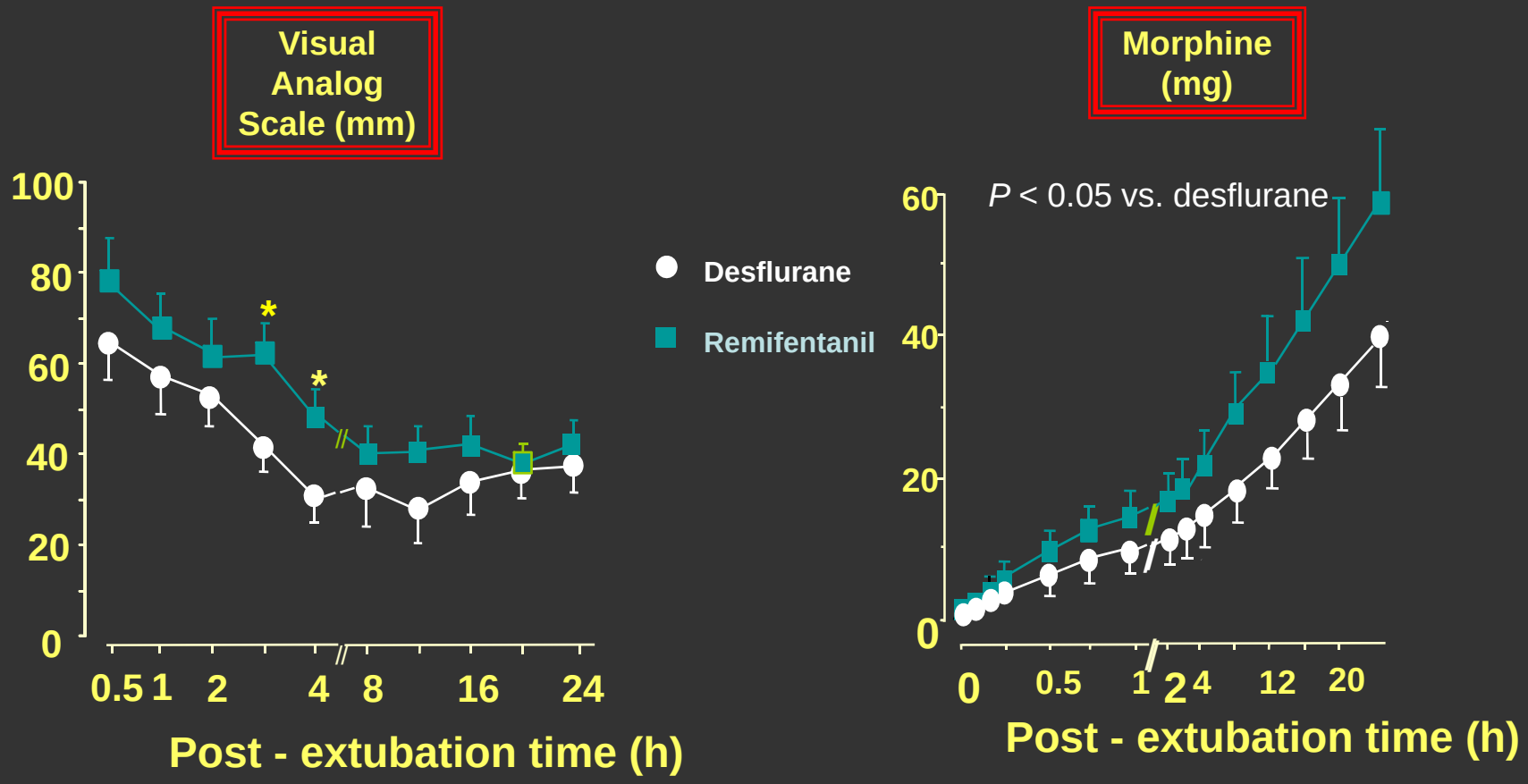


Anesthesiology
2000; 93:409–17

Acute Opioid Tolerance

Intraoperative Remifentanil Increases Postoperative Pain and Morphine Requirement

Bruno Guignard, M.D., Anne Elisabeth Bossard, M.D.,† Carole Coste, M.D.,‡ Daniel I. Sessler, M.D.,§ Claude Lebrault, M.D.,* Pascal Alfonsi, M.D.,* Dominique Fletcher, M.D.,* Marcel Chauvin, M.D.‖*



Guignard et al. Anesthesiology 2000

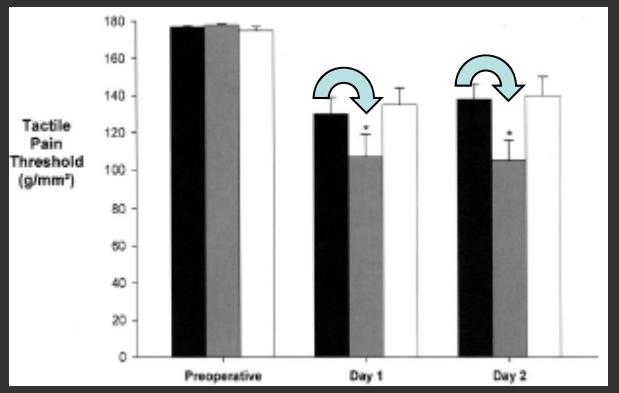
Anesthesiology 2005; 103:147–55

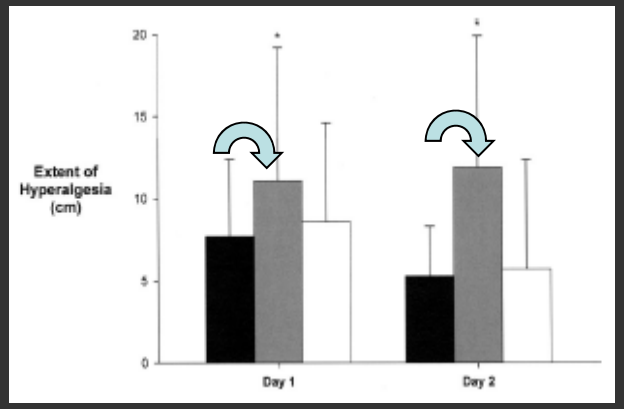
Remifentanil-induced Postoperative Hyperalgesia and Its Prevention with Small-dose Ketamine

Vincent Joly, M.D., Philippe Richebe, M.D.,† Bruno Guignard, M.D.,* Dominique Fletcher, M.D.,‡ Pierre Maurette, M.D.,§ Daniel I. Sessler, M.D.,‖ Marcel Chauvin, M.D.#*

	Small-dose Remifentanil (n = 25)	Large-dose Remifentanil (n = 25)	Large-dose Remifentanil–Ketamine (n = 24)
Remifentanil dose, mg	0.9 ± 0.3*	6.7 ± 3.1	6.5 ± 3.4
Desflurane, MAC/h	0.8 ± 0.2*	0.5 ± 0.2	0.6 ± 0.2
Ephedrine, No. of doses/No. of patients	9/17	10/13	50/15†
Final intraoperative temperature, °C	36.6 ± 0.7	36.3 ± 0.8	36.3 ± 0.9
Awakening time, min	14 ± 6	13 ± 5	14 ± 6
Extubation time, min	16 ± 6	14 ± 6	15 ± 4
Time to first postoperative morphine, min	35 (28–46)	24 (20–33)	41 (32–52)
Morphine given in PACU, mg	16 (10–24)	20 (17–27)	20 (14–23)
0–48 h cumulative postoperative morphine consumption, mg	68 (50–91)	86 (59–109)‡	62 (48–87)
Postoperative nausea and vomiting, No. of patients	7	8	8
Droperidol, No. of doses/No. of patients	8/7	8/8	8/8

Nociceptive threshold is lowered





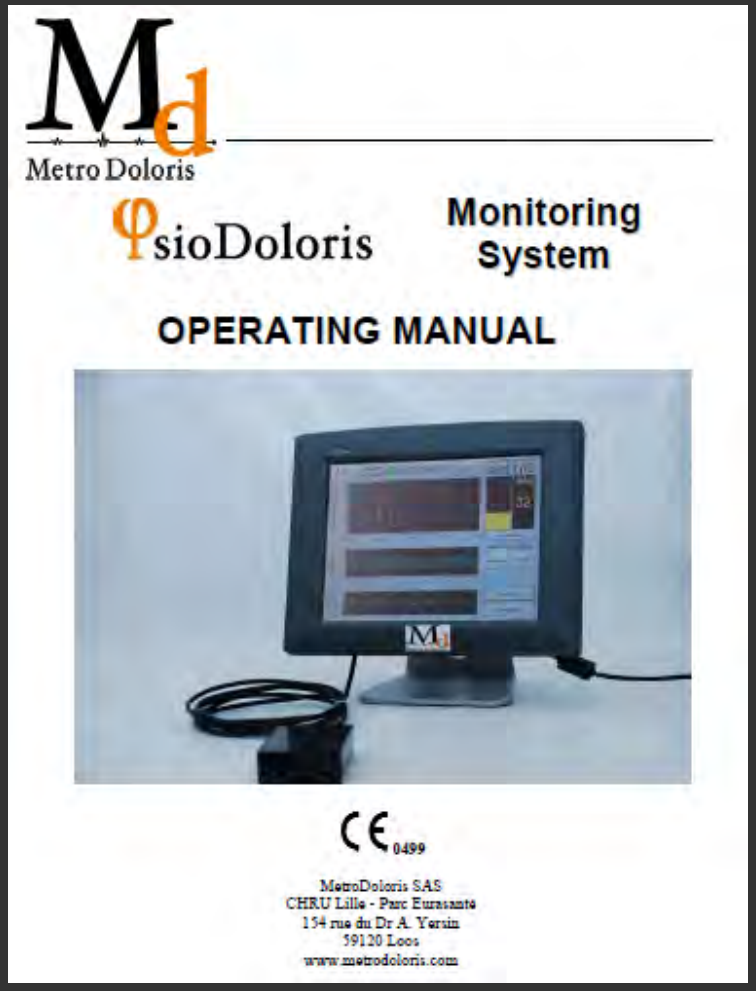
Area of Hyperalgesia is bigger

Joly, Richebé et al, Anesthesiology 2005

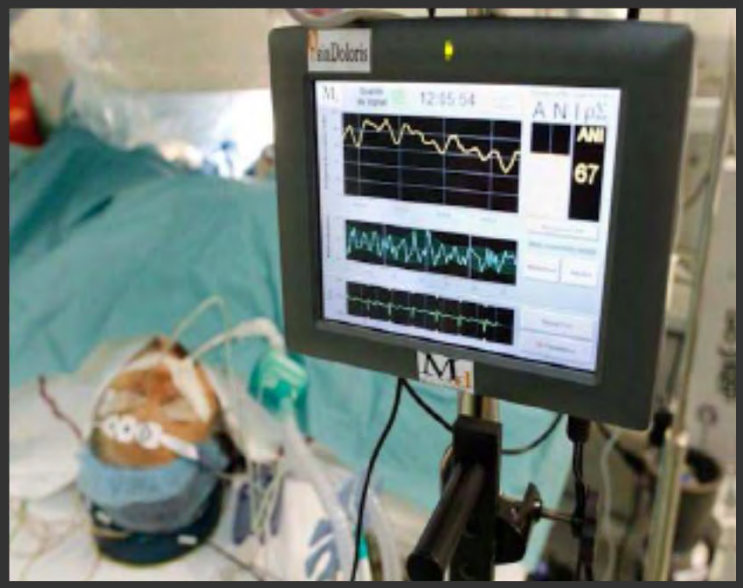
PhysioDoloris: a monitoring device for Analgesia / Nociception balance evaluation using Heart Rate Variability analysis.

R. Logier[1], M. Jeanne[1, 2], J. De jonckheere[1], A. Dassonneville[1], M. Delecroix[2], B. Tavernier[2]

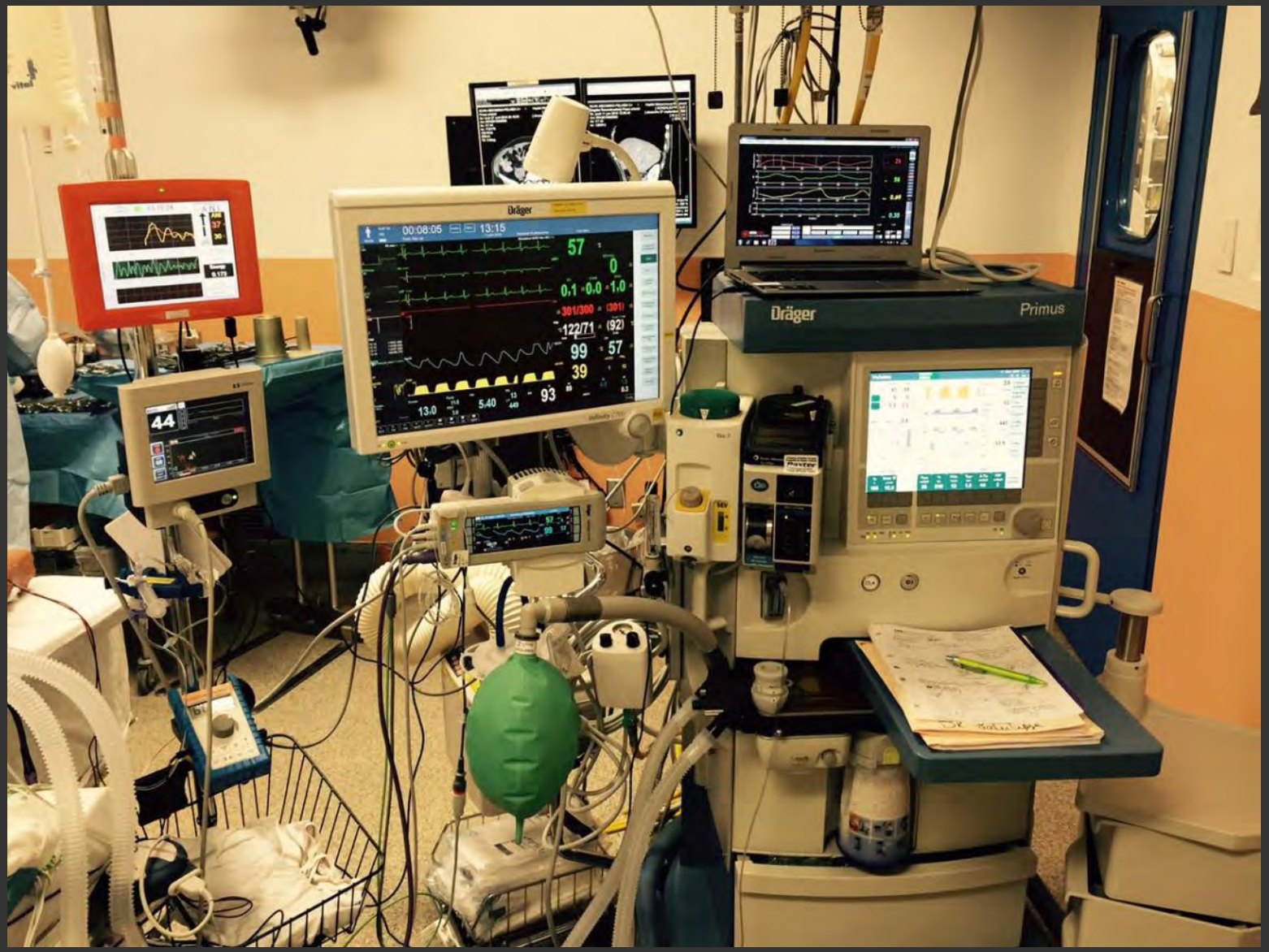
[1]INSERM CIC-IT 807, University Hospital of Lille, Institut Hippocrate, 2 avenue Oscar Lambret, 59037 LILLE Cedex, France
[2]Clinique d'Anesthésie Réanimation, University Hospital of Lille, H. Salengro, 2 avenue Oscar Lambret, 59037 LILLE Cedex, France

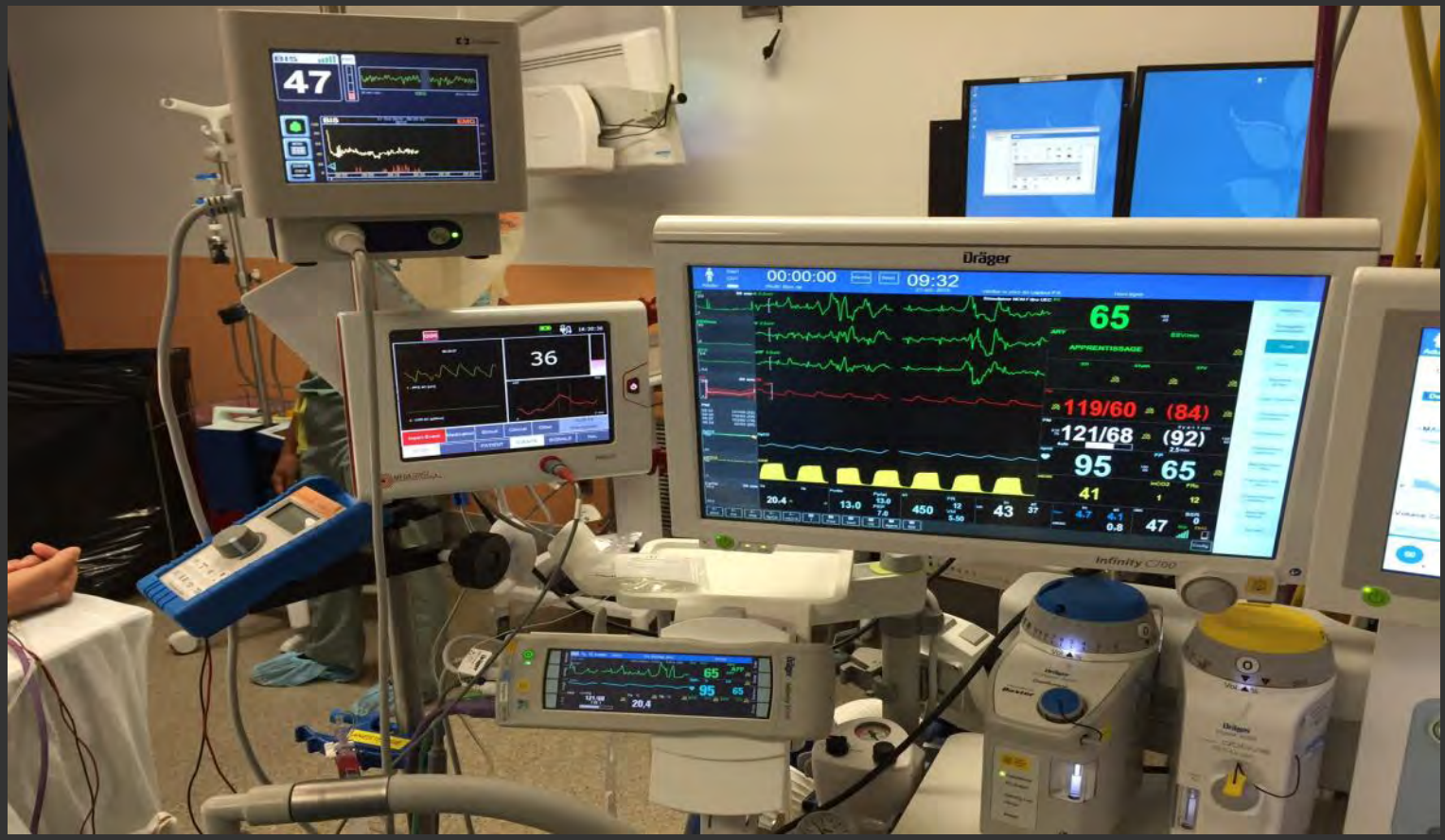


Mieux Monitorer



Mieux Monitorer

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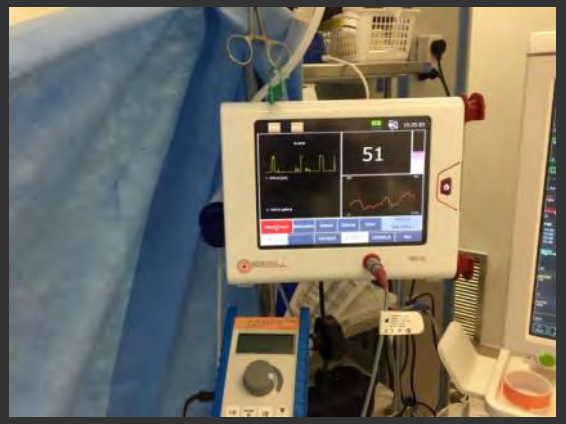
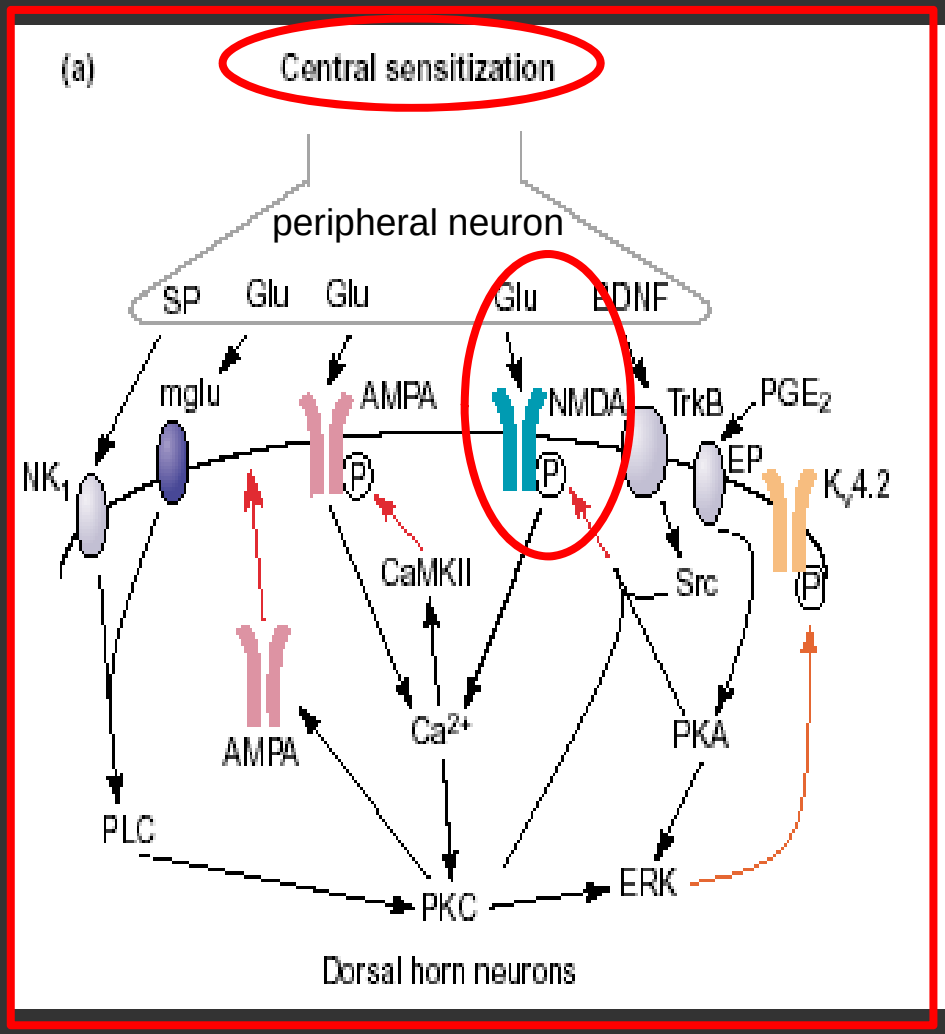
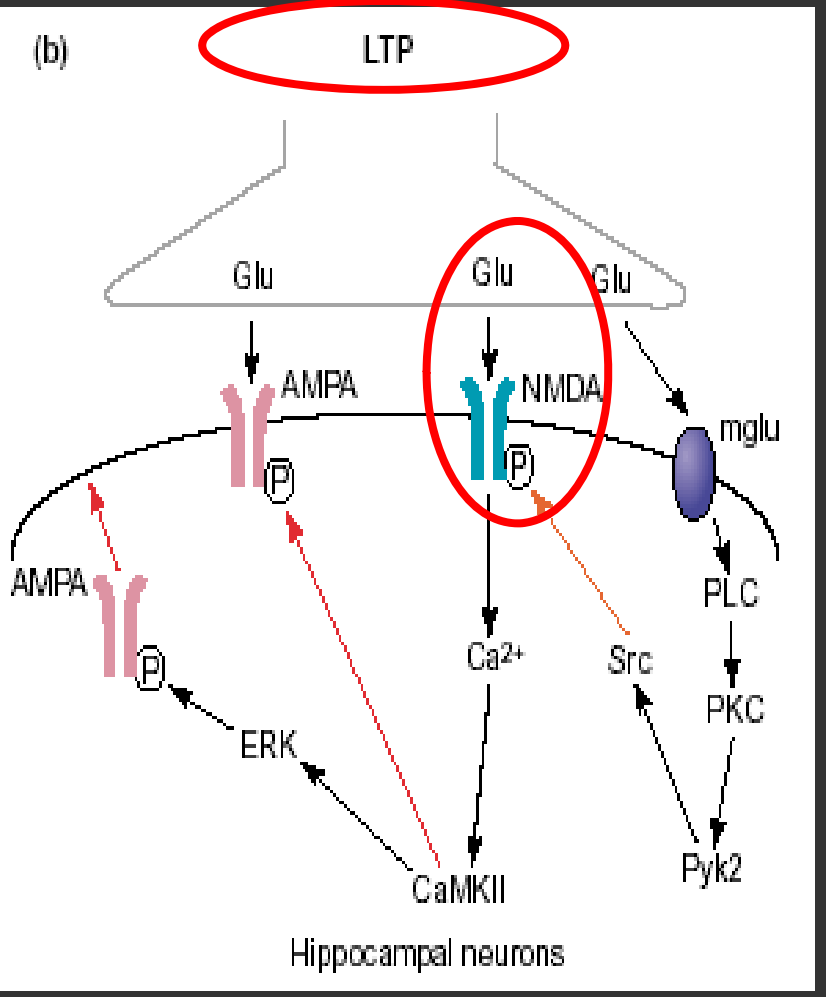

51

3/ Traitements Spécifiques

Sensibilisation Centrale





Ji RR et al, Trends in Neurosciences 2003

Ketamine

(Antagoniste des rec. NMDA)

Ketamine en anesthésie chez l'homme

Anesthesiology 2005; 103:147–55

Remifentanil-induced Postoperative Hyperalgesia and Its Prevention with Small-dose Ketamine

Vincent Joly, M.D., Philippe Richebe, M.D.,† Bruno Guignard, M.D.,* Dominique Fletcher, M.D.,‡ Pierre Maurette, M.D.,§ Daniel I. Sessler, M.D.,‖ Marcel Chauvin, M.D.#*

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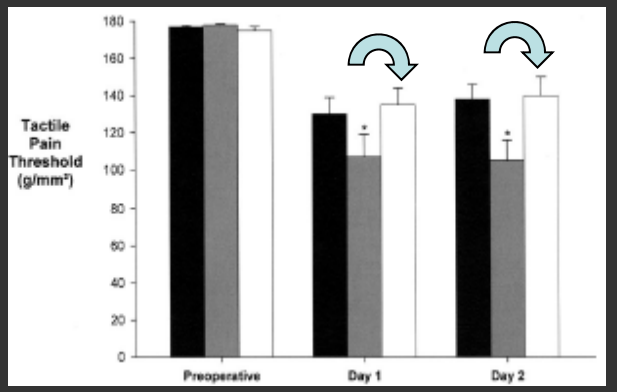

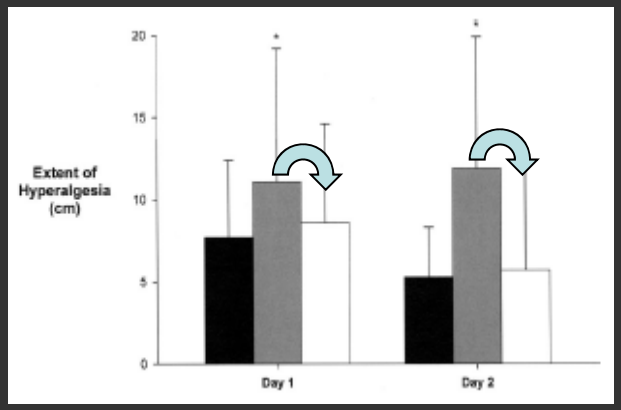

Joly, Richebé et al, Anesthesiology 2005

Ketamine and postoperative pain – a quantitative systematic review of randomised trials

Nadia Elia*, Martin R. Tramèr

Pain 113 (2005) 61–70

EBCAP Institute (Evidence-Based Critical care, Anaesthesia and Pain treatment), Division of Anaesthesiology, Geneva University Hospitals, 24 Rue Micheli-du-Crest, CH-1211 Geneva 14, Switzerland

Received 5 May 2004; received in revised form 10 September 2004; accepted 28 September 2004

Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review)

Acta Anaesthesiol Scand 2005; 49: 1405–1428
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R. F. Bell[1], J. B. Dahl[2], R. A. Moore[3] and E. Kalso[4]
[1]*Pain Clinic, Department of Anaesthesia and Intensive Care, Haukeland University Hospital and Department of Surgical Sciences, University of Bergen, Norway,* [2]*Department of Anaesthesia and Intensive Care, Glostrup University Hospital, Glostrup, Denmark,* [3]*Pain Research, Nuffield Department of Anaesthetics, University of Oxford, Oxford Radcliffe Hospitals, The Churchill, Oxford, UK and* [4]*Pain Clinic, Department of Anaesthesia and Intensive Care Medicine, Helsinki University Central Hospital, Helsinki, Finland*

Ketamine for Perioperative Pain Management

Sabine Himmelseher, M.D., Marcel E. Durieux, M.D., Ph.D.†*

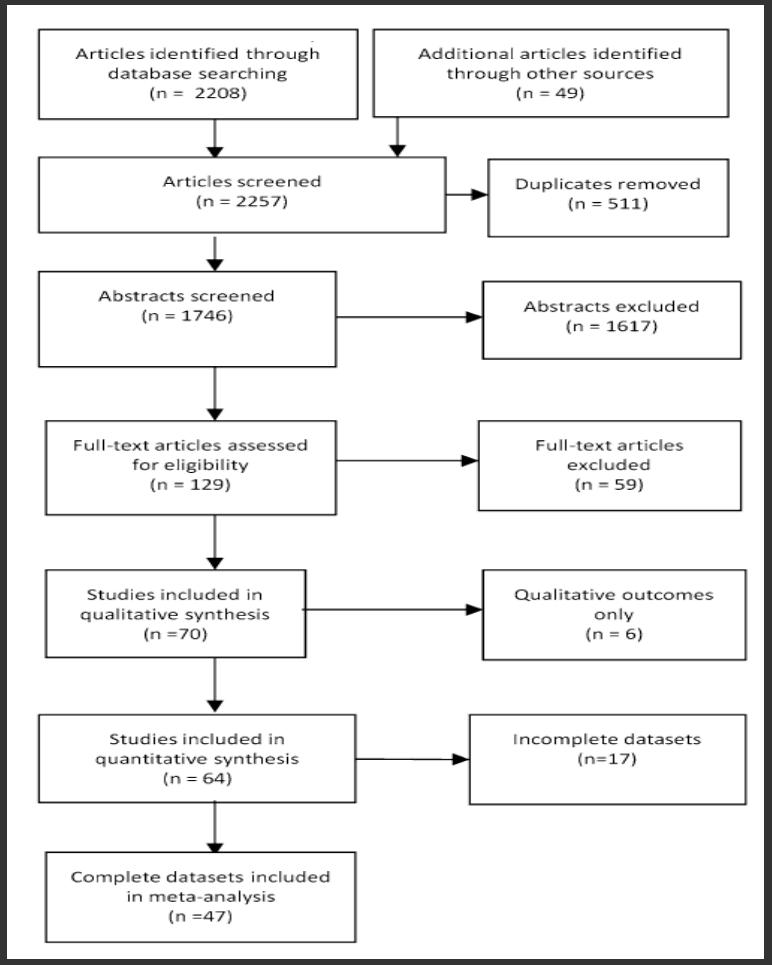
Anesthesiology 2005; 102:211–20

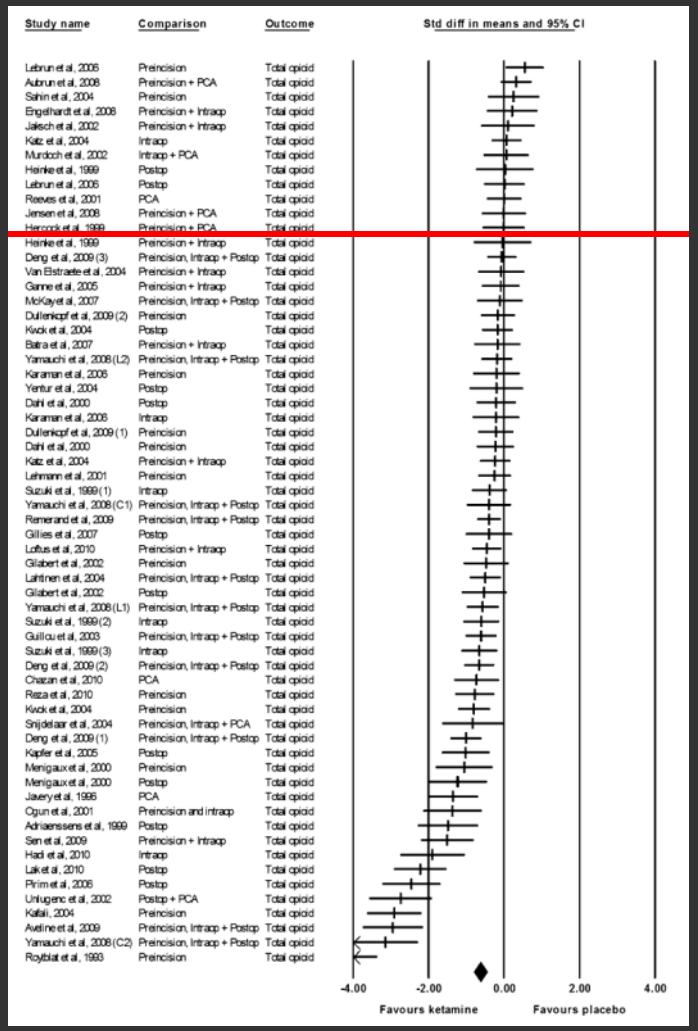
etc….

A systematic review of intravenous ketamine for postoperative analgesia

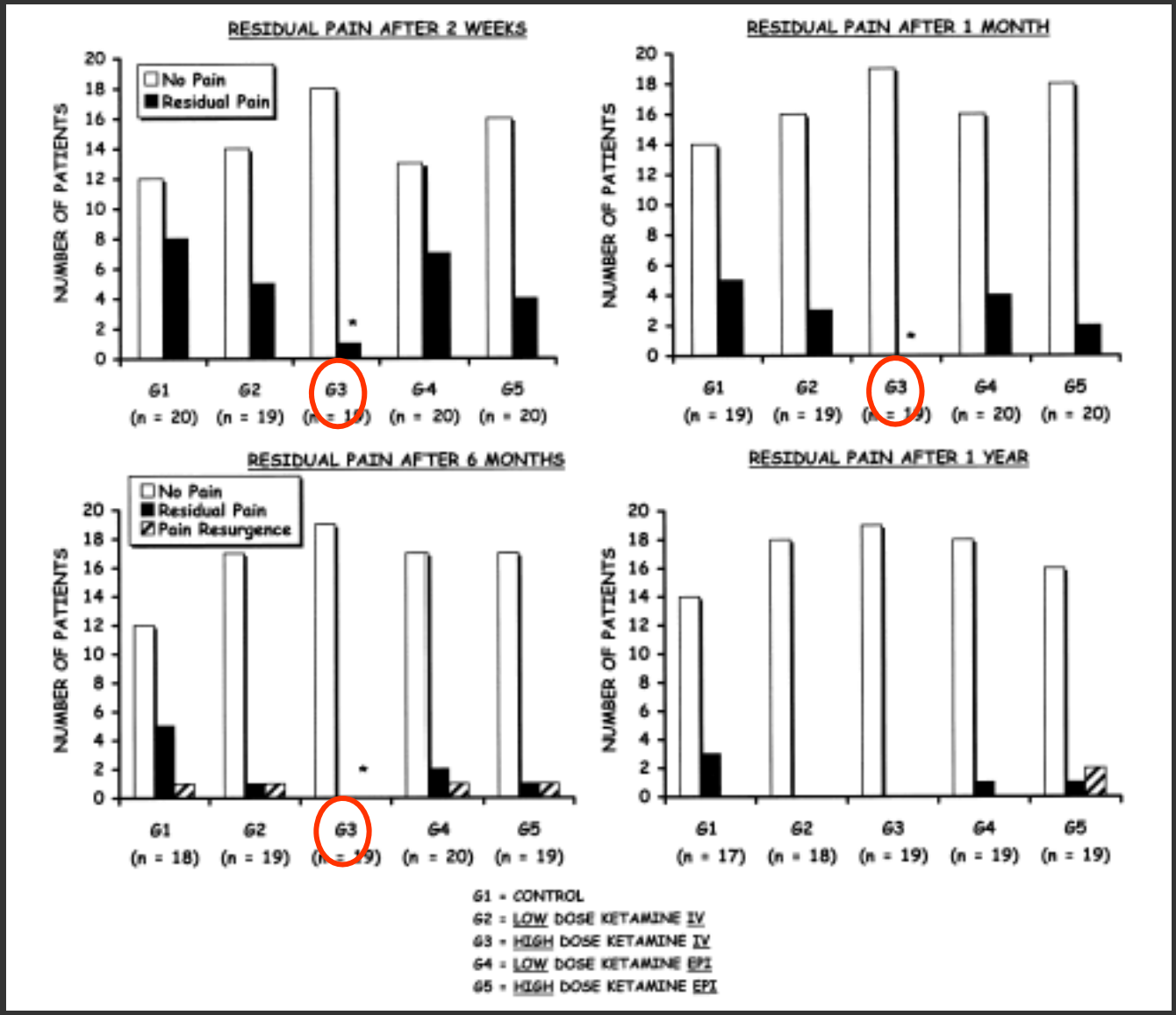
Kevin Laskowski, MD · Alena Stirling, MD · William P. McKay, MD · Hyun J. Lim, MD

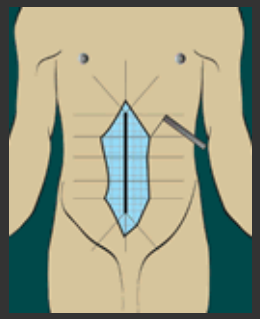
Can J Anesth/J Can Anesth (2011) 58:911–923





Ketamine in humans and Chronic Pain





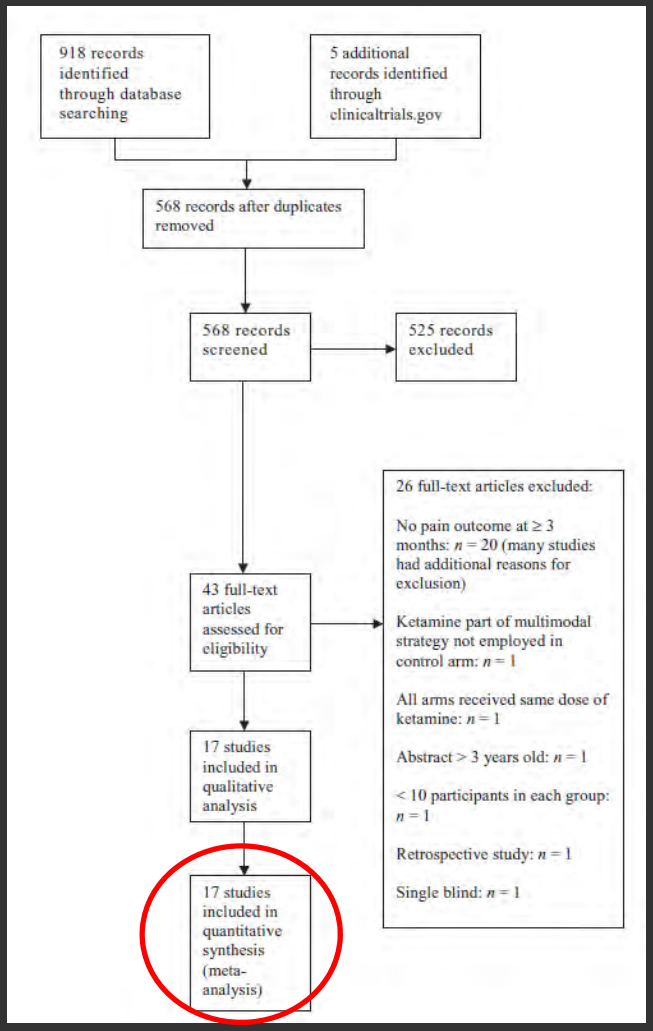
De Kock M. and al.

Pain, 2001. 92: 373-80

A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain

E. D. McNicol[1], R. Schumann[2] and S. Haroutounian[3]
[1]Department of Anesthesiology and Pharmacy, Tufts Medical Center, Boston, MA, USA, [2]Department of Anesthesiology, Tufts Medical Center, Boston, MA, USA and [3]Department of Anesthesiology, Washington University in St Louis, St Louis, MO, USA

Acta Anaesthesiol Scand 2014; *58*: 1199–1213



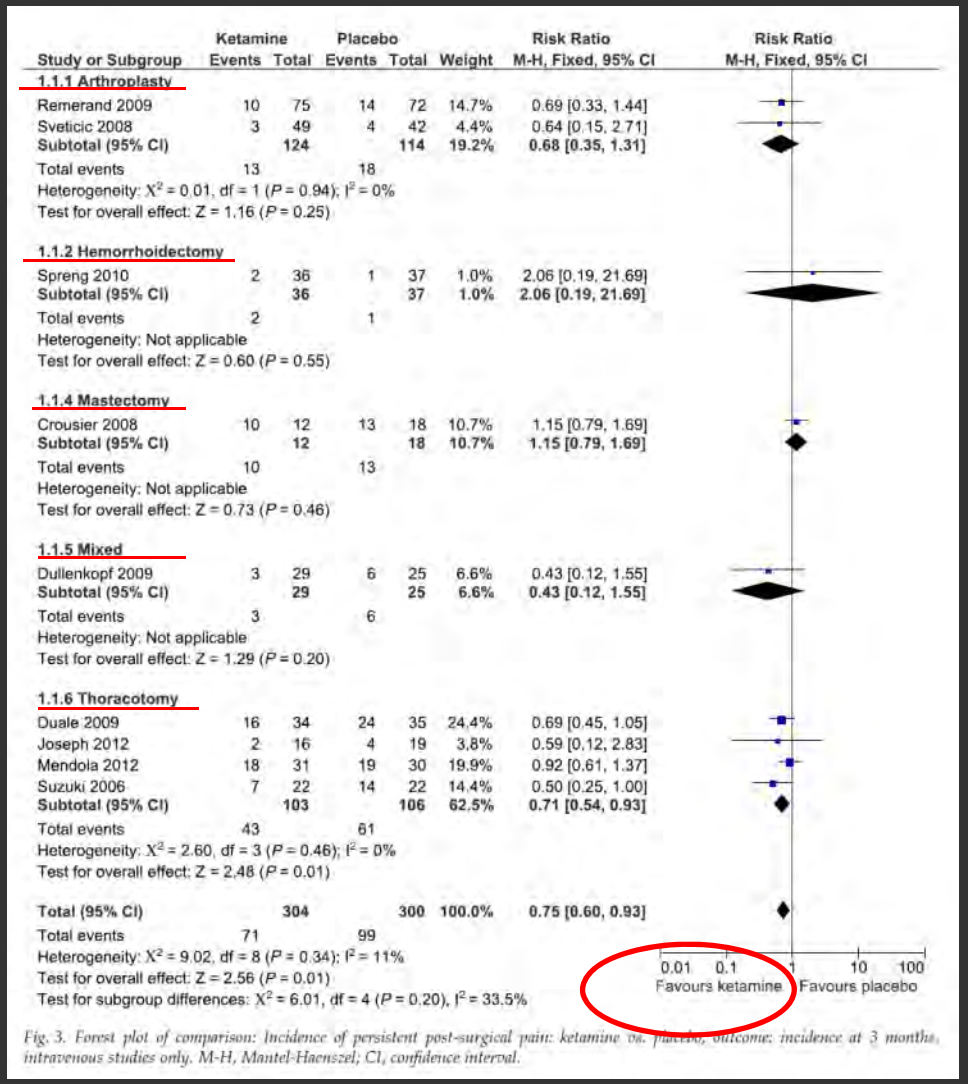
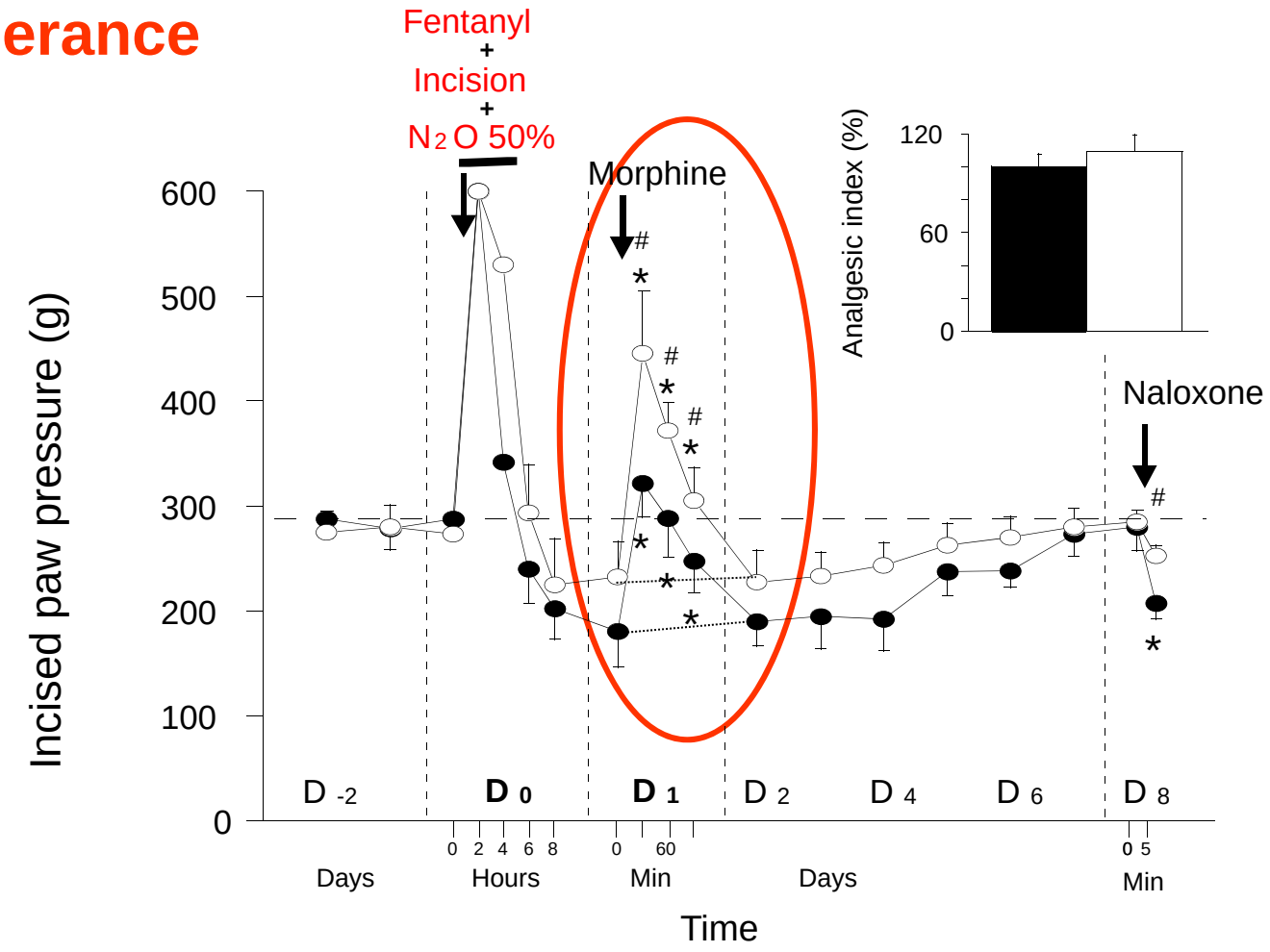


Fig. 3. Forest plot of comparison: Incidence of persistent post-surgical pain: ketamine vs. placebo, outcome: incidence at 3 months, intravenous studies only. M-H, Mantel-Haenszel; CI, confidence interval.

Protoxyde d’azote (N_2O)

N2O chez le rat…: un autre NMDA antagoniste

Decreases postop HA and Acute Morphine Tolerance

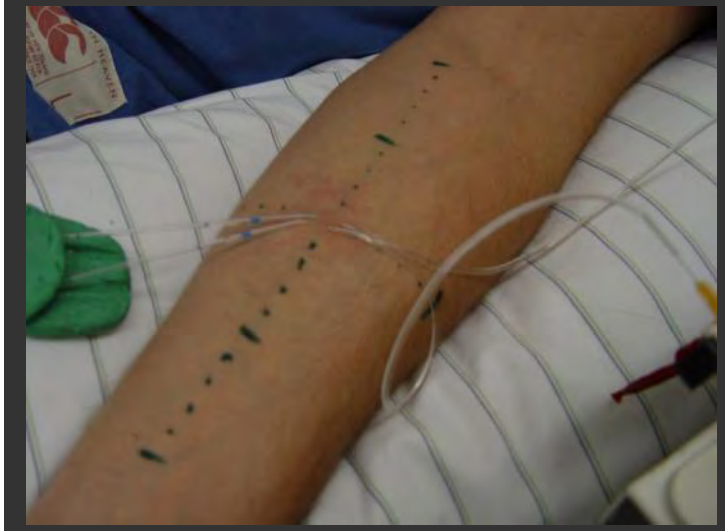


Richebé et al, Anesthesiology 2005

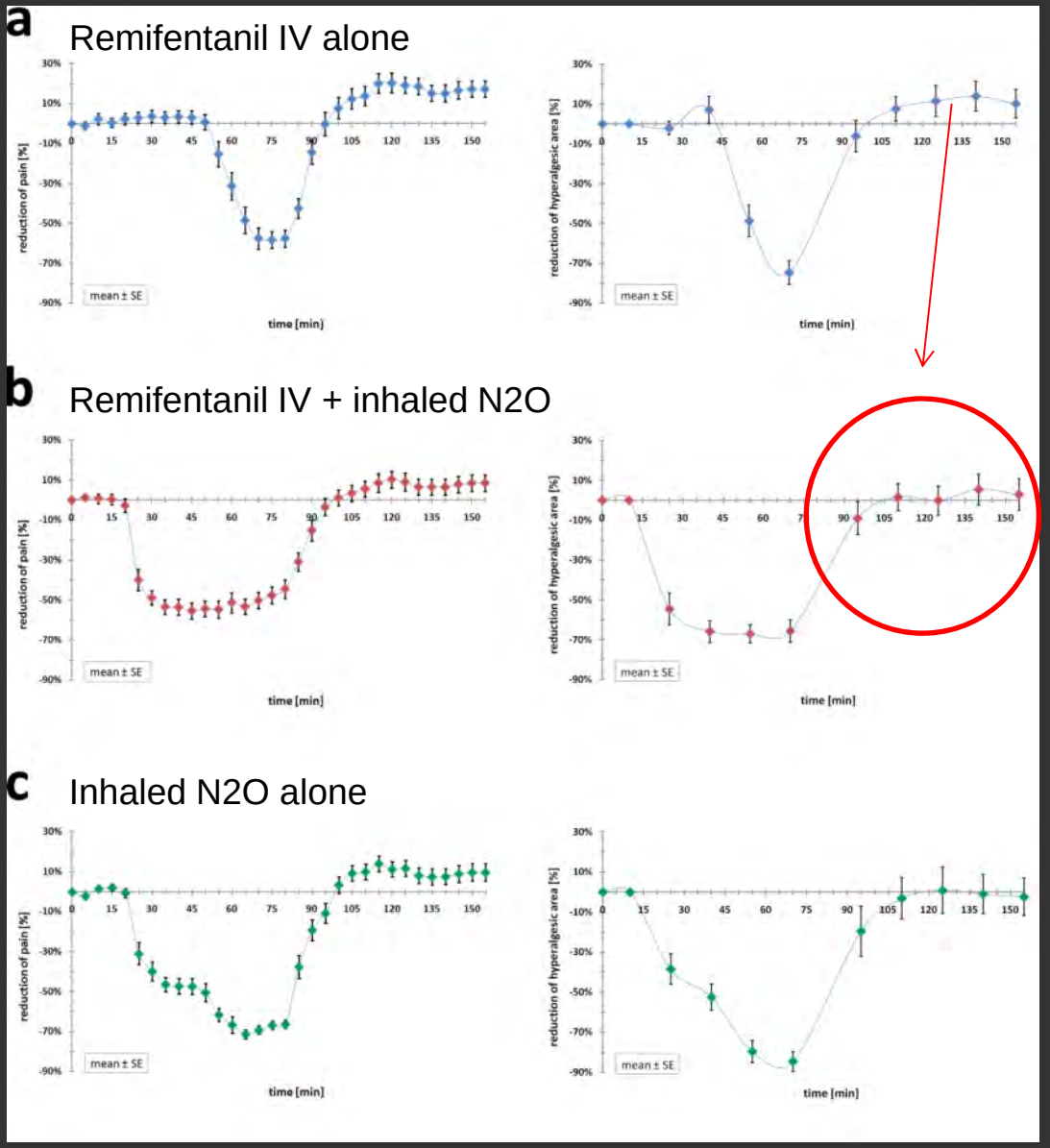
Collaboration avec W. Koppert

Erlangen – Nürnberg University

Germany



Richebé et al, in preparation



Avoidance of Nitrous Oxide for Patients Undergoing Major Surgery

A Randomized Controlled Trial

the ENIGMA Trial Group
Paul S. Myles

Anesthesiology 2007; 107:221–31

Conclusions: **Avoidance of nitrous oxide and the concomitant increase in inspired oxygen concentration decreases the incidence of complications after major surgery, but does not significantly affect the duration of hospital stay. The routine use of nitrous oxide in patients undergoing major surgery should be questioned.**

Chronic postsurgical pain after nitrous oxide anesthesia

PAIN® 152 (2011) 2514–2520

Matthew T.V. Chan [a,*], Alex C.M. Wan [a], Tony Gin [a], Kate Leslie [b,c], Paul S. Myles [d,e]

Factors associated with mild-to-moderate chronic postsurgical pain.

Factors	Patients (n)	Patients with severe chronic postsurgical pain	Univariate		Multivariate	
			OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age (y)	423	62.4 ± 12.5 (n = 46)	1.01 (0.99–1.05)	.24		
Gender						
Male	235	23 (9.8%)	Reference			
Female	188	23 (12.2%)	1.29 (0.69–2.37)	.44		
Wound type						
Others	199	17 (7.6%)	Reference			
Supraumbilical wound	224	29 (14.6%)	2.08 (1.10–3.91)	.03		
Wound length (cm)	423	19.3 ± 3.7 (n = 46)	1.17 (1.10–1.25)	.01	1.14 (1.04–1.26)	0.04
Minimally invasive surgery						
No	363	44 (12.1%)	Reference			
Yes	60	2 (3.3%)	0.25 (0.06–1.00)	.05		
Regional block						
No	352	42 (11.9%)	Reference			
Yes	71	4 (5.6%)	0.44 (0.15–1.27)	.08		
Severe acute postoperative pain						
No	378	26 (6.9%)	Reference			
Yes	45	20 (44.4%)	10.8 (5.32–22.0)	<.001	9.10 (2.58–32.1)	0.001
Anxiety[a]	423	11 (2–17) (n = 46)	2.38 (1.92–2.94)	<.001	2.28 (1.76–2.95)	<0.001
Wound infection						
No	365	28 (7.7%)	Reference			
Yes	58	18 (31.0%)	5.42 (2.75–10.7)	.001	4.80 (1.48–15.6)	0.01
Nitrous oxide administration						
No	209	31 (14.8%)	Reference			
Yes	214	15 (7.0%)	0.43 (0.23–0.83)	.01	0.48 (0.33–0.93)	0.04
Pre-existing pain problem elsewhere						
No	403	42 (10.4%)	Reference			
Yes	20	4 (20.0%)	2.15 (0.69–6.73)	.26		
Inspired oxygen concentration[b]						
21%–40%	43	7 (16.3%)	Reference			
41%–60%	60	9 (15.0%)	1.28 (0.48–3.42)	.63		
>61%	106	14 (13.2%)	1.16 (0.47–2.87)	.75		

Values are n (%), mean ± standard deviation, or median (range).

[a] Range of possible scores 0 (lowest level) to 21.

[b] This analysis included only those patients receiving nitrous oxide-free anesthesia.

Mais aucune étude prospective pour N2O et PPSP…

Magnésium

**(Bloqueur « naturel »
des rec. NMDA au repos…)**

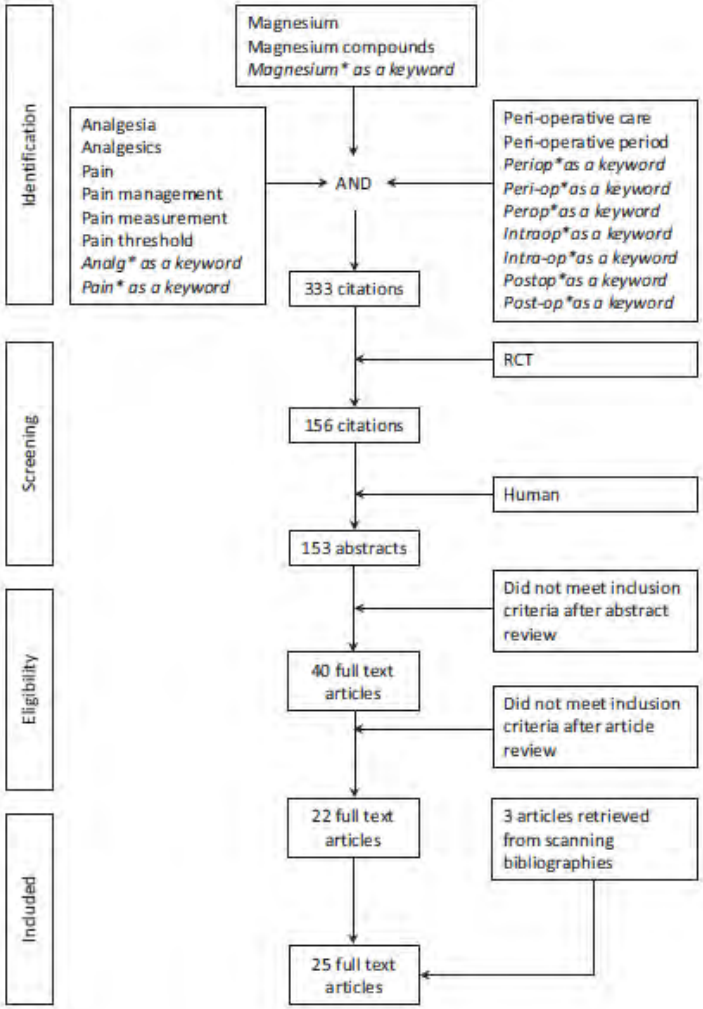
NMDA receptors

Krystal et al, Pharmacol. Ther., 2003

Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis

E. Albrecht,[1] K. R. Kirkham,[1] S. S. Liu[2] and R. Brull[3]

Anaesthesia 2012
Toronto, Canada

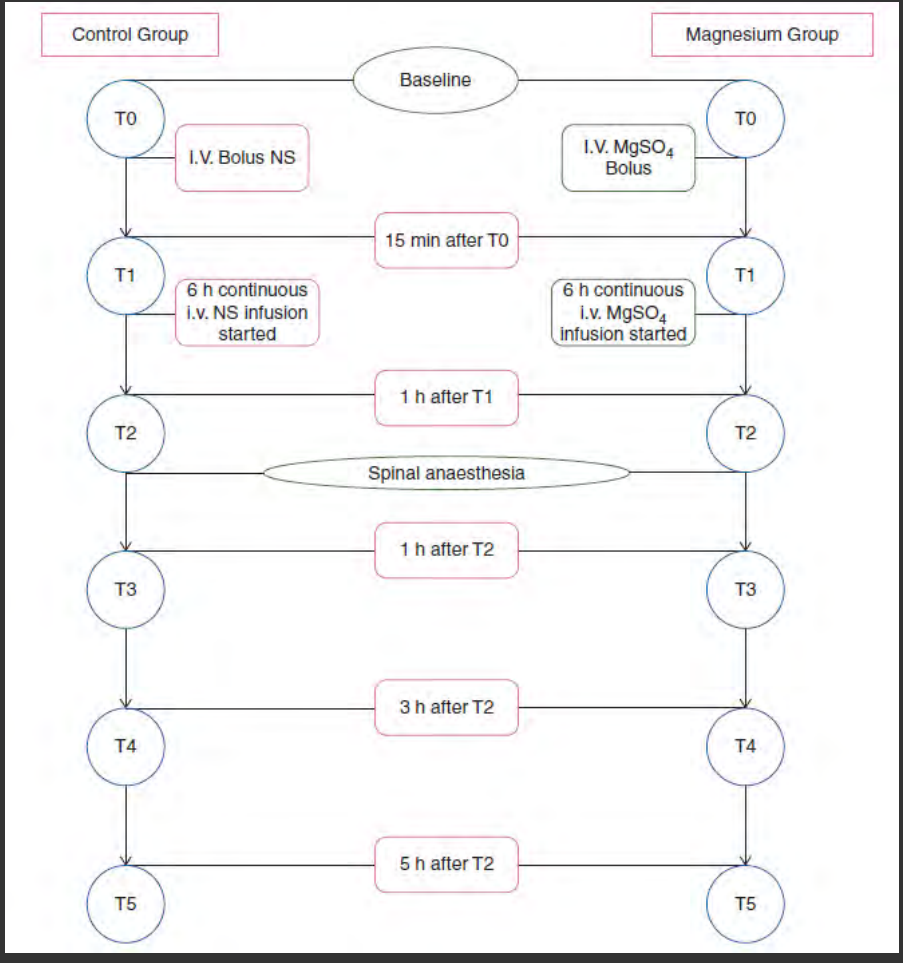


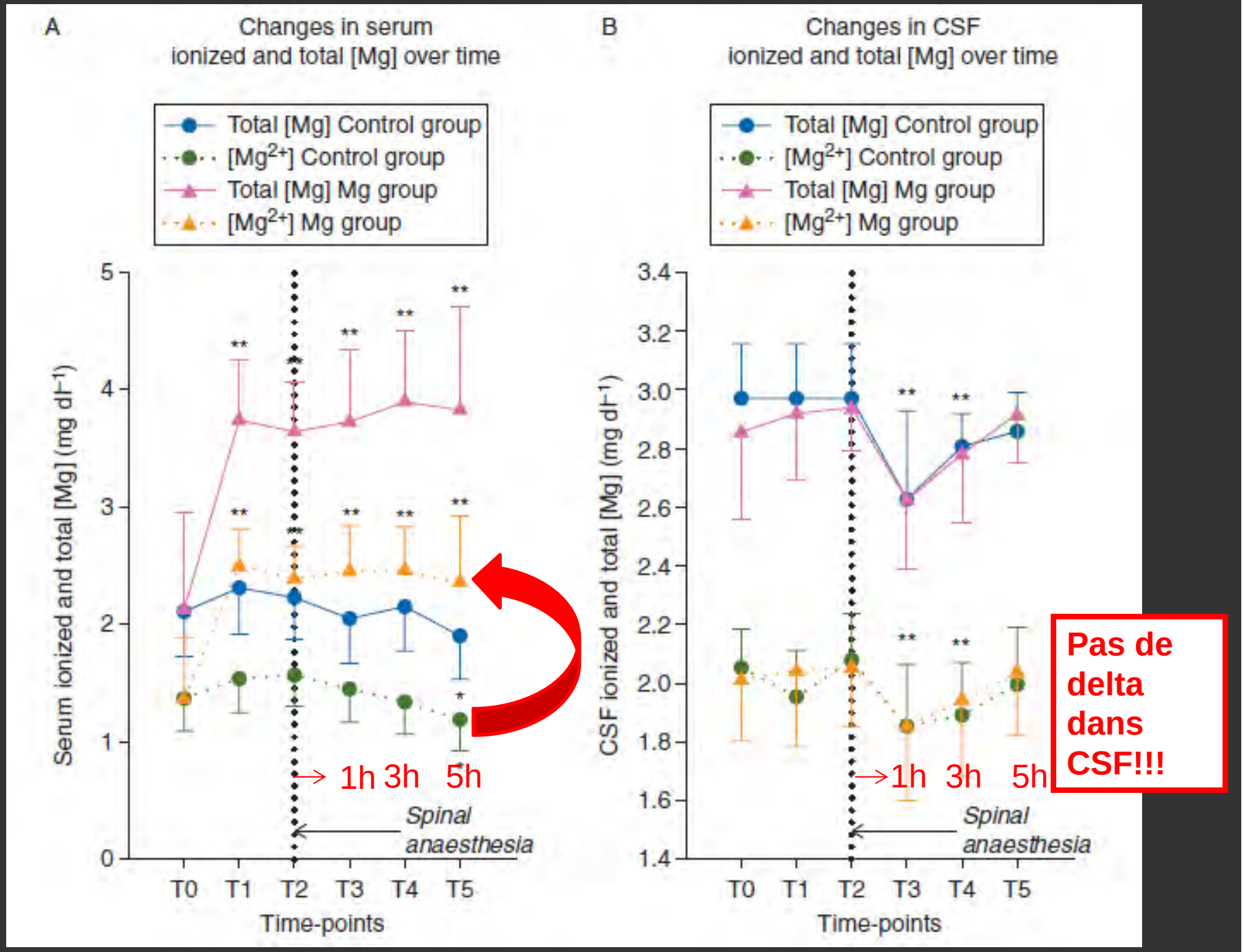
" We conclude that peri-operative intravenous magnesium reduces opioid consumption, and to a lesser extent, pain scores, in the first 24h postoperatively, without any reported serious adverse effects".

Changes in cerebrospinal fluid magnesium levels in patients undergoing spinal anaesthesia for hip arthroplasty: does intravenous infusion of magnesium sulphate make any difference? A prospective, randomized, controlled study

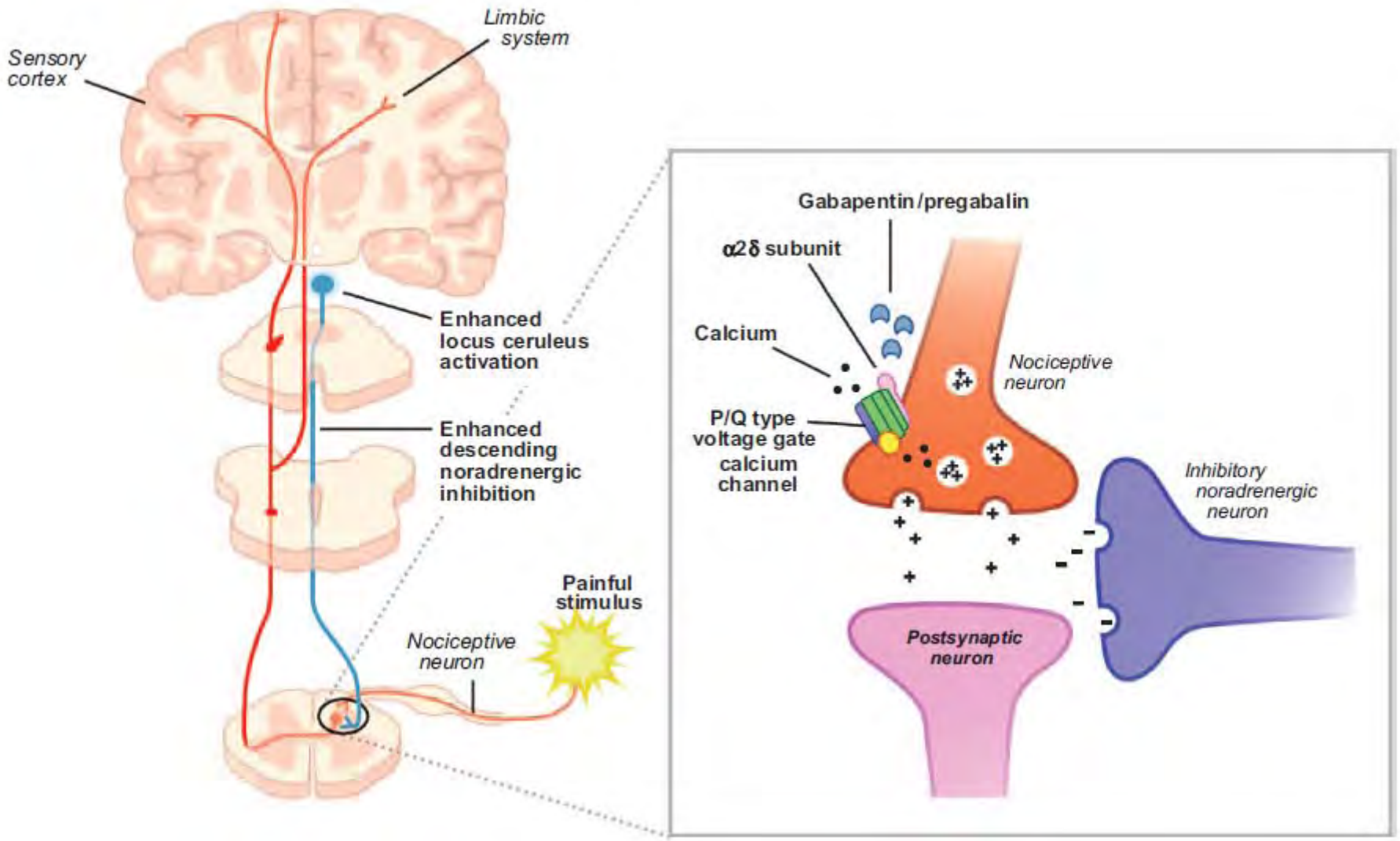
M. Mercieri[1*], R. A. De Blasi[1], S. Palmisani[3], S. Forte[1], P. Cardelli[2], R. Romano[4], G. Pinto[1] and R. Arcioni[1]

British Journal of Anaesthesia **109** (2): 208–15 (2012)

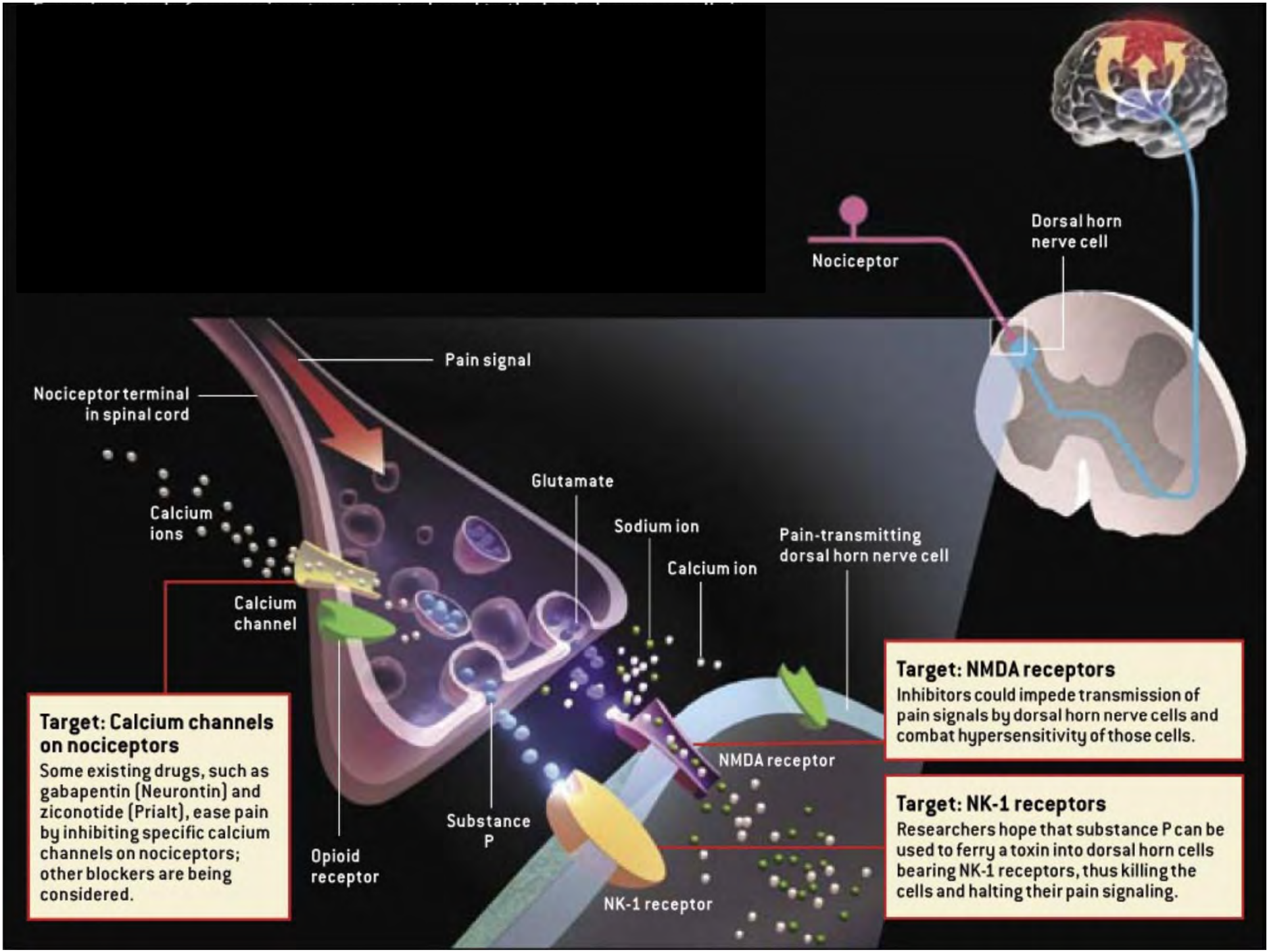



A
Changes in serum
ionized and total [Mg] over time
Total [Mg] Control group
[Mg2+] Control group
Total [Mg] Mg group
[Mg2+] Mg group
Serum ionized and total [Mg] (mg dl−1)
5
4
3
2
1
0
**
*
1h 3h 5h
Spinal
anaesthesia
T0 T1 T2 T3 T4 T5
Time-points
B
Changes in CSF
ionized and total [Mg] over time
Total [Mg] Control group
[Mg2+] Control group
Total [Mg] Mg group
[Mg2+] Mg group
CSF ionized and total [Mg] (mg dl−1)
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
**
1h 3h 5h
Spinal
anaesthesia
T0 T1 T2 T3 T4 T5
Time-points
Pas de
delta
dans
CSF!!!

Gabapentine, Pregabaline



Anesthesiology 2013; 119:1215-21


Nociceptor
Dorsal horn nerve cell
Pain signal
Nociceptor terminal in spinal cord
Calcium ions
Glutamate
Sodium ion
Calcium ion
Pain-transmitting dorsal horn nerve cell
Calcium channel
Target: Calcium channels on nociceptors
Some existing drugs, such as gabapentin (Neurontin) and ziconotide (Prialt), ease pain by inhibiting specific calcium channels on nociceptors; other blockers are being considered.
NMDA receptor
Target: NMDA receptors
Inhibitors could impede transmission of pain signals by dorsal horn nerve cells and combat hypersensitivity of those cells.
Substance P
Opioid receptor
NK-1 receptor
Target: NK-1 receptors
Researchers hope that substance P can be used to ferry a toxin into dorsal horn cells bearing NK-1 receptors, thus killing the cells and halting their pain signaling.

The Prevention of Chronic Postsurgical Pain Using Gabapentin and Pregabalin: A Combined Systematic Review and Meta-Analysis

AA 2012

Hance Clarke, MSc, MD, FRCPC,*†‡ Robert P. Bonin, PhD,§ Beverley A. Orser, MD, PhD, FRCPC,†‡ Marina Englesakis, BA MLIS,‖ Duminda N. Wijeysundera, MD, PhD, FRCPC,*‡¶# and Joel Katz, PhD**

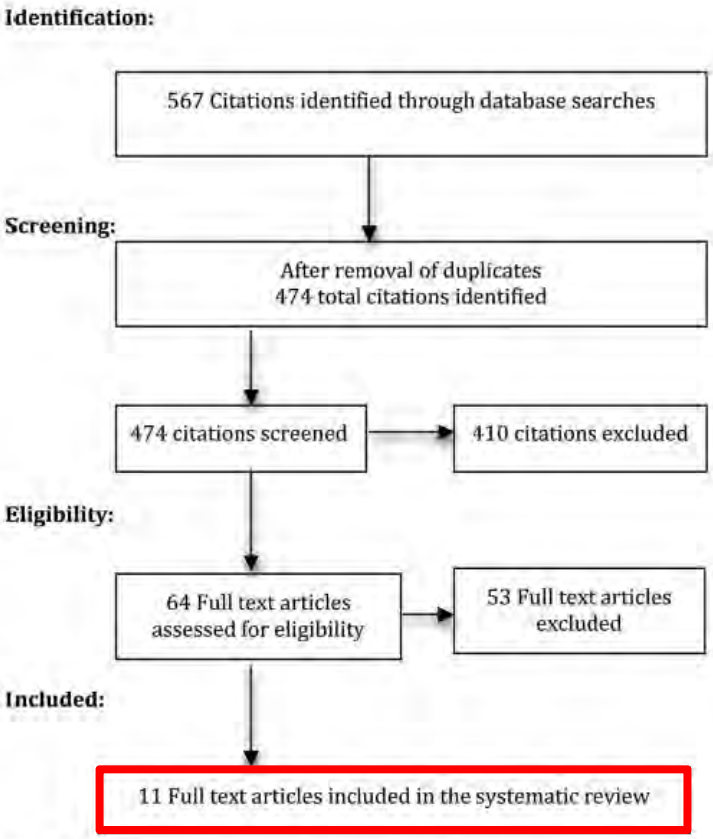


Figure 1. Selection process for systematic review.

- 6 des études sur la **GABAPENTINE** ont démontré une réduction seulement modérée dans le développement des PPSP (pooled odds ratio [OR] 0.52; 95% confidence interval [CI], 0.27 to 0.98; P = 0.04),
- Les 2 études sur la **PREGABALINE** ont rapporté une grande réduction des PPSP (pooled OR 0.09; 95% CI, 0.02 to 0.79; P = 0.007),
- **CONCLUSIONS :** La présente métaanalyse supporte l'utilisation des gabapentinoides pour réduire les PPSP

Perioperative Gabapentinoids

Choice of Agent, Dose, Timing, and Effects on Chronic Postsurgical Pain

Peter C. Schmidt, M.D.,* Gabriela Ruchelli, B.A.,† Sean C. Mackey, M.D., Ph.D.,‡
Ian R. Carroll, M.D., M.S. Epi.§

Anesthesiology 2013; 119:1215-21

It should now be generally accepted that the gabapentinoids are effective in reducing *immediate* postoperative pain and opioid consumption. The clinician should recognize that this has been better established for gabapentin than pregabalin. However, larger studies with both longer follow-up and improved patient retention will be needed to more definitively test the efficacy of these agents to reduce the emergence of *chronic* postsurgical pain. When more studies on both pregabalin and gabapentin have been done assessing the effect of the gabapentinoids on chronic pain, another meta-analysis should examine the strength of the body of evidence as a whole. However, the currently available data support the conclusion that such a preventative analgesic effect is likely.

Table 3. Studies Finding an Effect on Prolonged Postoperative Pain

Authors	N	Surgery	Gabapentinoid Dose	Findings
Fassoulaki *et al.*[35]	60	Abdominal hysterectomy	Gabapentin 400 mg every 6 h beginning preoperatively and continuing for 5 days	Decreased incidence and intensity of pain at 1 month
Sen *et al.*[43]	60	Herniorrhaphy	Gabapentin 1,200 mg 1 h before surgery	Decreased pain scores at 1, 3, and 6 months
Sen *et al.*[42]	60	Abdominal hysterectomy	Gabapentin 1,200 mg 1 h before surgery	Decreased incidence of incisional pain at 1, 3, and 6 months
Brogly *et al.*[31]	50	Thyroidectomy	Gabapentin 1,200 mg 2 h before surgery	Decreased incidence of neuropathic pain at 6 months
Amr and Yousef[30]	150	Mastectomy	Gabapentin 300 mg/day starting the night before surgery and continuing for 10 days	Decreased incidence of burning pain at 6 months
Fassoulaki *et al.*[36]	75	Breast surgery for cancer	Gabapentin 1,200 mg/day for 10 days after surgery	Decreased incidence of burning pain at 3 months
Buvanendran *et al.*[26]	240	Total knee arthroplasty	Pregabalin 300 mg 1–2 h before surgery and a 14-day taper after surgery	Decreased incidence of neuropathic pain at 3 and 6 months
Pesonen *et al.*[41]	70	Cardiac surgery	Pregabalin 150 mg 1 h before surgery and 150 mg daily for 5 days	Decreased incidence of pain with movement at 3 months
Burke and Shorten[32]	40	Lumbar discectomy	Pregabalin 300 mg 90 min before surgery and 150 mg at 12 and 24 h after surgery	Decreased pain scores and improved function at 3 months

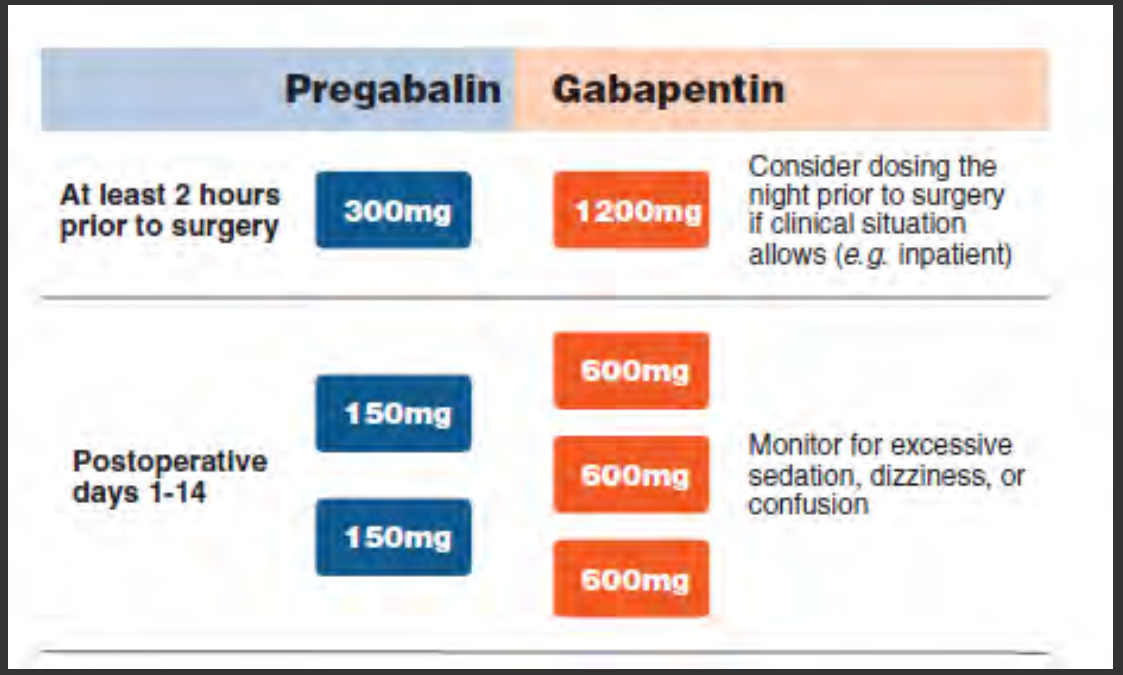
Table 4. Studies Finding No Effect on Prolonged Postoperative Pain

Authors	N	Surgery	Gabapentinoid Dose	Findings
Ucak *et al.*[44]	40	Coronary artery bypass graft	Gabapentin 1,200 mg before and for 2 days after surgery	No difference in pain scores at 1 and 3 months (all scores ≤1)
Clarke *et al.*[33]	126	Total hip arthroplasty	Gabapentin 600 mg 1–2 h before surgery or 600 mg immediately postoperatively	No difference in presence or severity of pain at 6 months
Moore *et al.*[39]	44	Cesarean section	Gabapentin 600 mg 1 h before surgery	No difference in persistent pain or abnormal wound sensation at 3 months
Nikolajsen *et al.*[40]	41	Lower limb amputation	Gabapentin titrated to 2,400 mg/day beginning on the first postoperative day and continuing for 30 days	No difference in phantom or stump pain at 3 and 6 months
Gianesello *et al.*[37]	60	Lumbar laminectomy and fusion	Pregabalin 300 mg 1 h before surgery for 2 days after surgery	No difference in pain scores at 3 months and 1 yr (quality of life measures improved at 3 months)
Kim *et al.*[38]	94	Endoscopic thyroidectomy	Pregabalin 150 mg 1 h before surgery and at 12 h after surgery	No difference in pain or hypoesthesia at 3 months
Fassoulaki *et al.*[35]	80	Abdominal hysterectomy or myomectomy	Pregabalin 150 mg every 8 h starting the afternoon before surgery and continuing 5 days	No difference in presence of pain, analgesic intake, or wound sensation at 1 and 3 months

Table 1. Dosage Adjustments for Renal Impairment

Creatinine Clearance, ml/min	Maximum Daily Pregabalin Dose, mg	Maximum Daily Gabapentin Dose, mg
≥60	600	3,600
30–60	300	1,400
15–30	150	700
15	75	300

Recommended doses :



Lidocaine I.V.

Perioperative Intravenous Lidocaine Decreases the Incidence of Persistent Pain After Breast Surgery

Anca Grigoras, MD, Peter Lee, MD, Faisal Sattar, BSc, and George Shorten, PhD

Clin J Pain • Volume 28, Number 7, September 2012

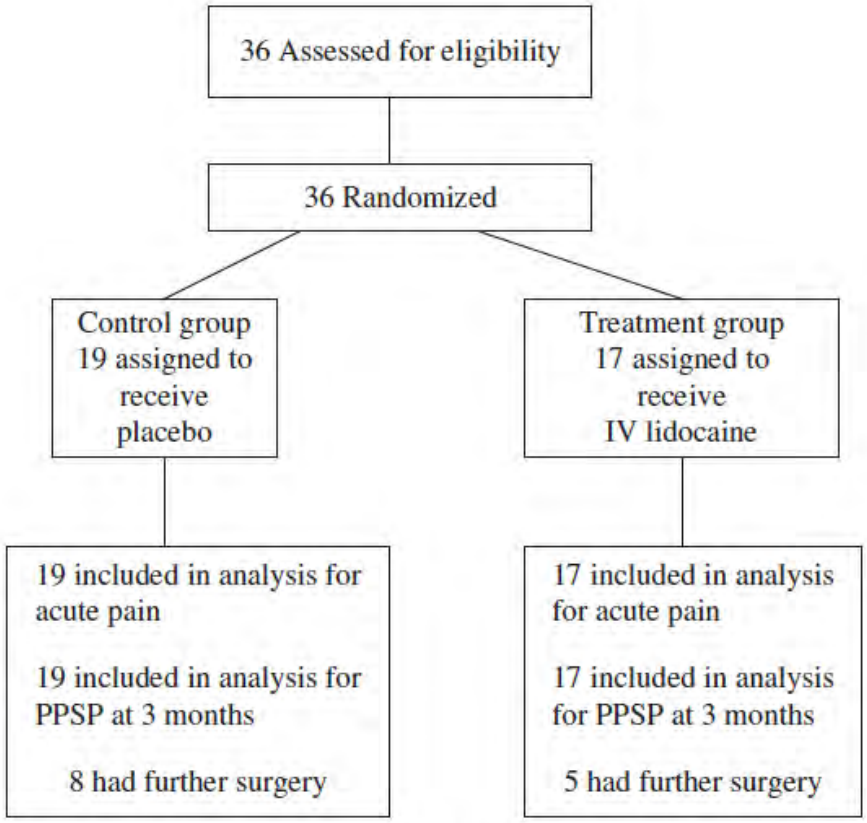


FIGURE 1. The flow diagram of patients studied. PPSP indicates persistent postsurgical pain.

Immediately after orotracheal intubation, patients of the lidocaine group (L) received an IV bolus of lidocaine (1.5 mg/kg in 10 min) followed by a continuous IV infusion at 1.5 mg/kgh. The infusion was stopped 60 minutes after skin closure. Patients in the control group (C) received an equivalent saline regimen. The anesthetist, surgeon, and nursing staff were all blinded to the group allocations.

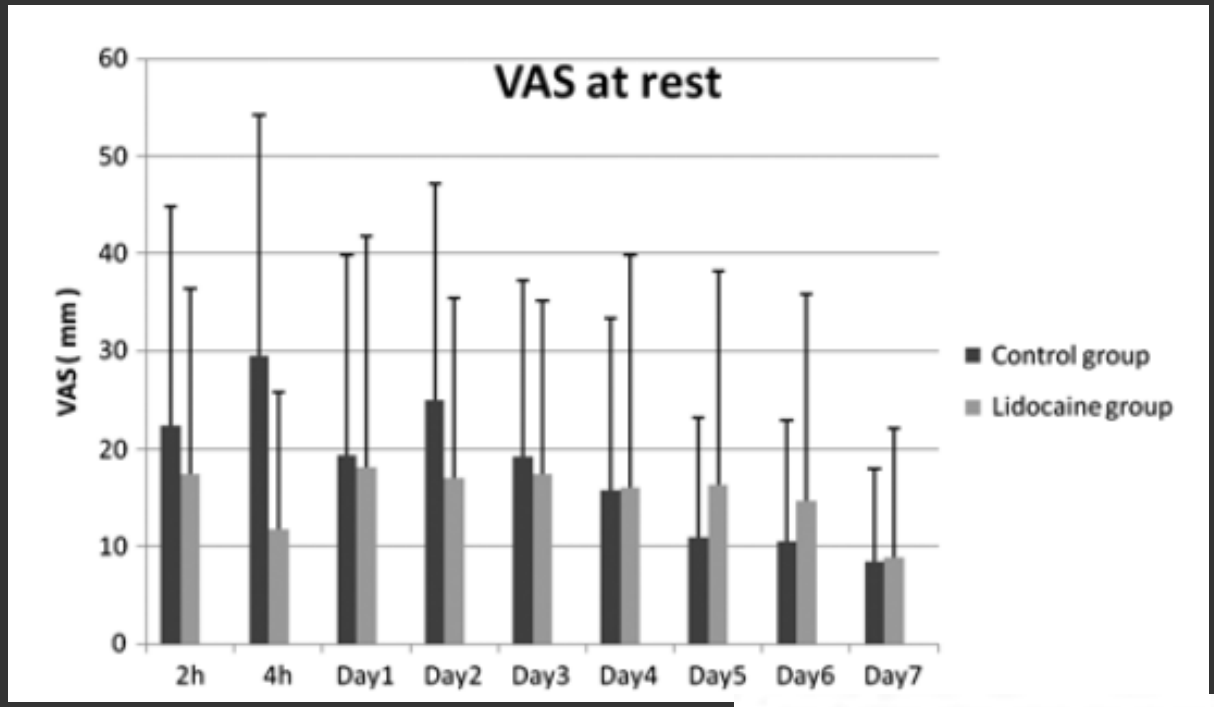


TABLE 3. Postoperative Morphine Consumption

	Lidocaine Group (n = 17)	Control Group (n = 19)	*P*
Analgesia request in 24 h	13/17 (76.5%)	14/19 (73.3%)	0.849
Morphine 2 h	2.6 (± 2.5)	3.0 (± 3.8)	0.869
Morphine 4 h	0.5 (± 1.3)	1.4 (± 2.3)	0.179
Morphine 24 h	2.1 (± 5.1)	4.2 (± 10.3)	0.623
Morphine 2 d	0.3 (± 1.2)	3.1 (± 8.7)	0.310
Morphine 3 d	0.2 (± 0.7)	2.3 (± 5.7)	0.310
Morphine 4 d	0	0.5 (± 2.3)	0.344
Morphine 5 d	0	0	1.000
Morphine 6 d	0	0	1.000
Morphine 7 d	0	0	1.000

TABLE 4. Chronic Pain Assessment (Patients' Characteristics at 3 mo Follow-up)

	Lidocaine Group (n = 17)	Control Group (n = 19)	*P*
PPSP	2 (11.8%)	9 (47.4%)	0.031*
S-PRI	1.1 (± 3.9)	1.4 (± 3.2)	0.049*
A-PRI	0.1 (± 0.5)	0.7 (± 2.1)	0.196
T-PRI	1.2 (± 4.4)	2.1 (± 5.3)	0.039*
PPI-VAS	2.6 (± 7.5)	14.6 (± 22.5)	0.025*
Overall pain intensity	0.2 (± 0.5)	0.9 (± 1.4)	0.023*
HADS anxiety	5.4 (± 4.9)	2.8 (± 4.2)	0.108
HADS depression	5.4 (± 4.4)	3.0 (± 3.4)	0.079
PCS rumination	1.3 (± 2.4)	1.7 (± 3.8)	0.971
PCS magnification	1.1 (± 2.5)	0.9 (± 1.7)	0.719
PCS helplessness	1.5 (± 3.1)	1.4 (± 3.7)	0.580
PCS total	3.9 (± 7.1)	4.0 (± 9.1)	0.631
Required analgesia	1 (5.9%)	2 (10.5%)	1.000
Worse with movement	0	8 (42.1%)	0.003*
Interfere with activities	1 (5.9%)	5 (10.5%)	0.182
Hyperalgesia (cm)	0.2 (± 0.8)	3.2 (± 4.5)	0.002*

*Statistically significant difference.

Data are presented as mean ± SD or number of patients.

Extent of hyperalgesia is expressed as area of hyperalgesia (cm^2) divided by length of surgical incision (cm).

A-PRI indicates affective pain rating index; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; PPI-VAS, present pain intensity-visual analog scale; PPSP, persistent postsurgical pain; S-PRI, sensory pain rating index; T-PRI, total pain rating index.

CONCLUSION

Pre-op.	Intra-op.	Post-op.	Tardif Post-op.
Epidurale ou Bloc nerveux	Epidurale ou Bloc nerveux	Epidurale ou Bloc nerveux	
P.O. pregabaline	i.v. ketamine i.v. lidocaine	i.v. ketamine 2 jours i.v. lidocaine P.O. pregabaline	
Multimodale Pre-op Analgesie APAP NSAIDs ?	Multimodale Intra-op Analgesie i.v. APAP i.v. NSAIDs?	Multimodale Post-op Analgesie i.v. puis P.O. APAP i.v. puis P.O. NSAIDs? i.v. opioids (PCA morphine, HM…)	

Du préop à aussi longtemps que possible…

Merci pour votre attention!