OPIOID-INDUCED HYPERALGESIA

Department of Anesthesiology

DEFINITION

- Pain

“Unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

1979 - The International Association for the Study of Pain (IASP)

PAIN PATHWAY

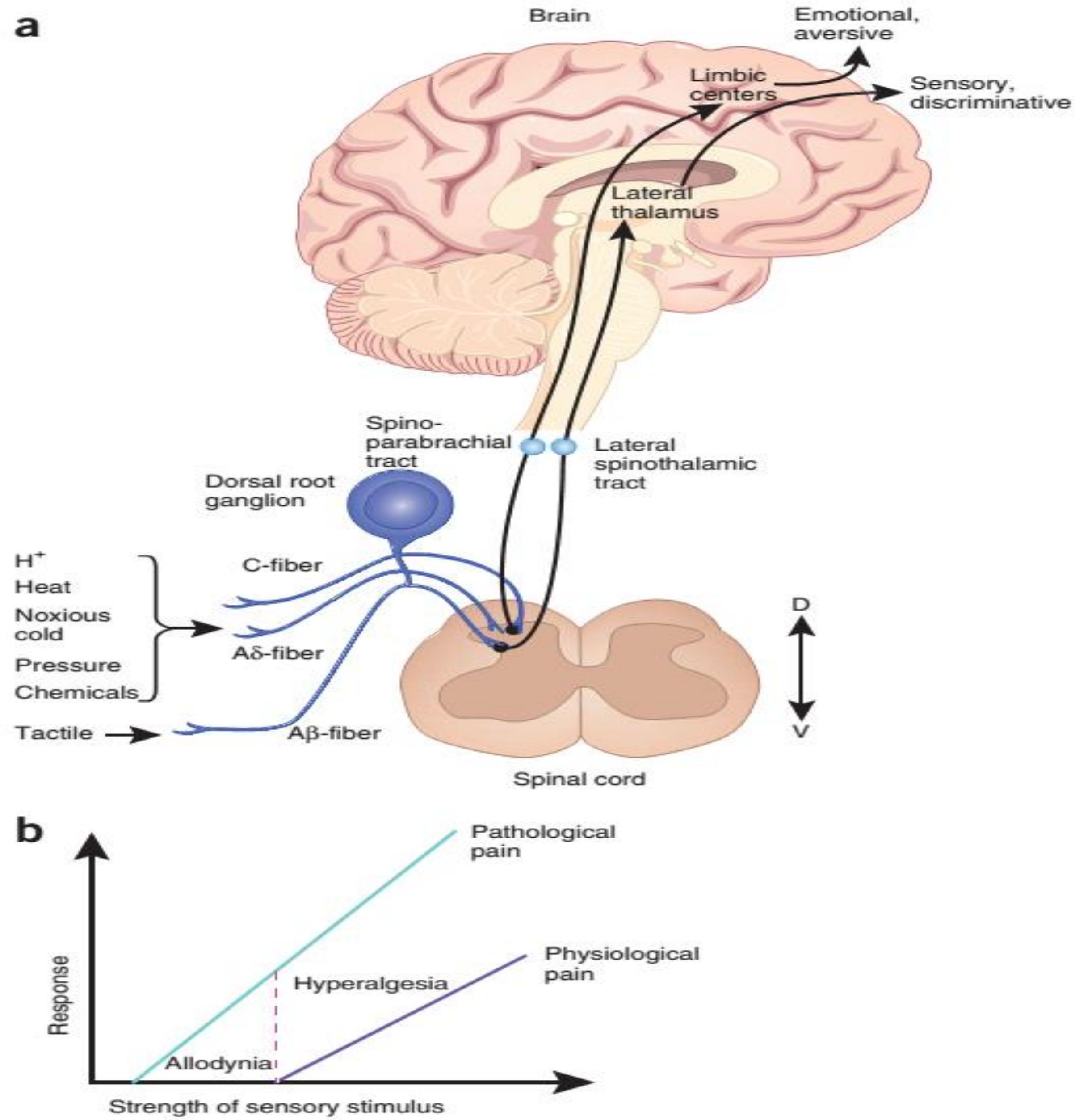


Figure 1 Pain circuits. (**a**,**b**) A schematic overview of the main circuits mediating physiological pain (**a**) and some manifestations of chronic pain (**b**).

Nat Med. 2010 Nov;16(11):1258-66.

DEFINITION

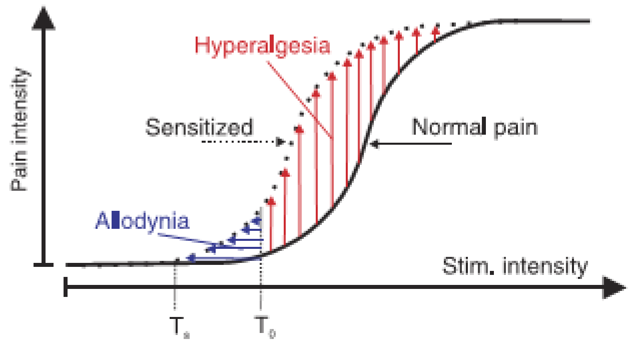
- Hyperalgesia:

"a state of increased intensity of pain sensation induced by either noxious or ordinarily non-noxious stimulation of peripheral tissue"

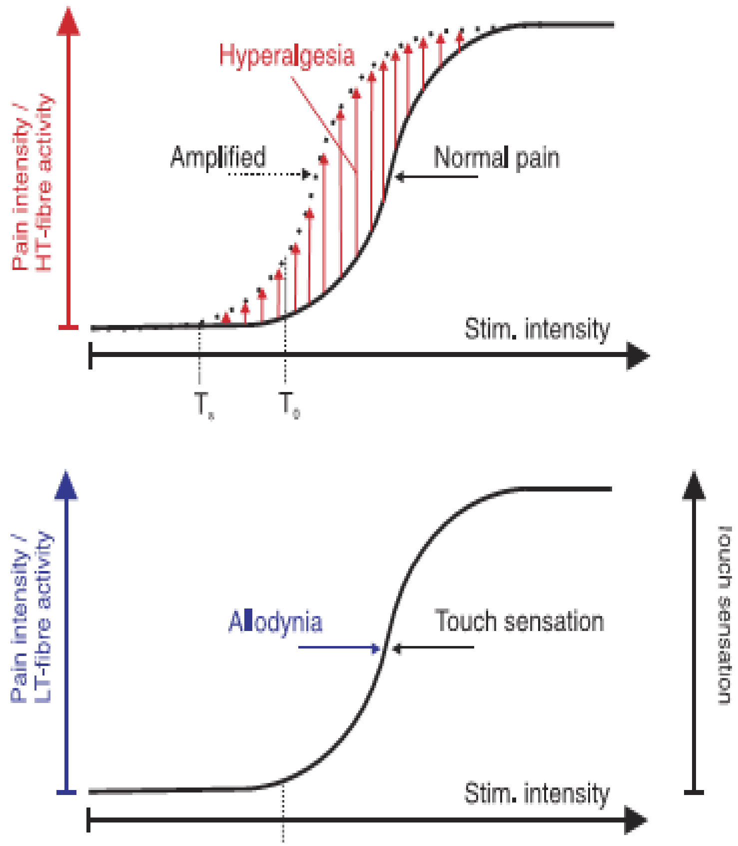
Hardy JD et al J Clin Invest 29: 115–140, 1950

Hyperalgesia is increased pain from a stimulus that normally provokes pain

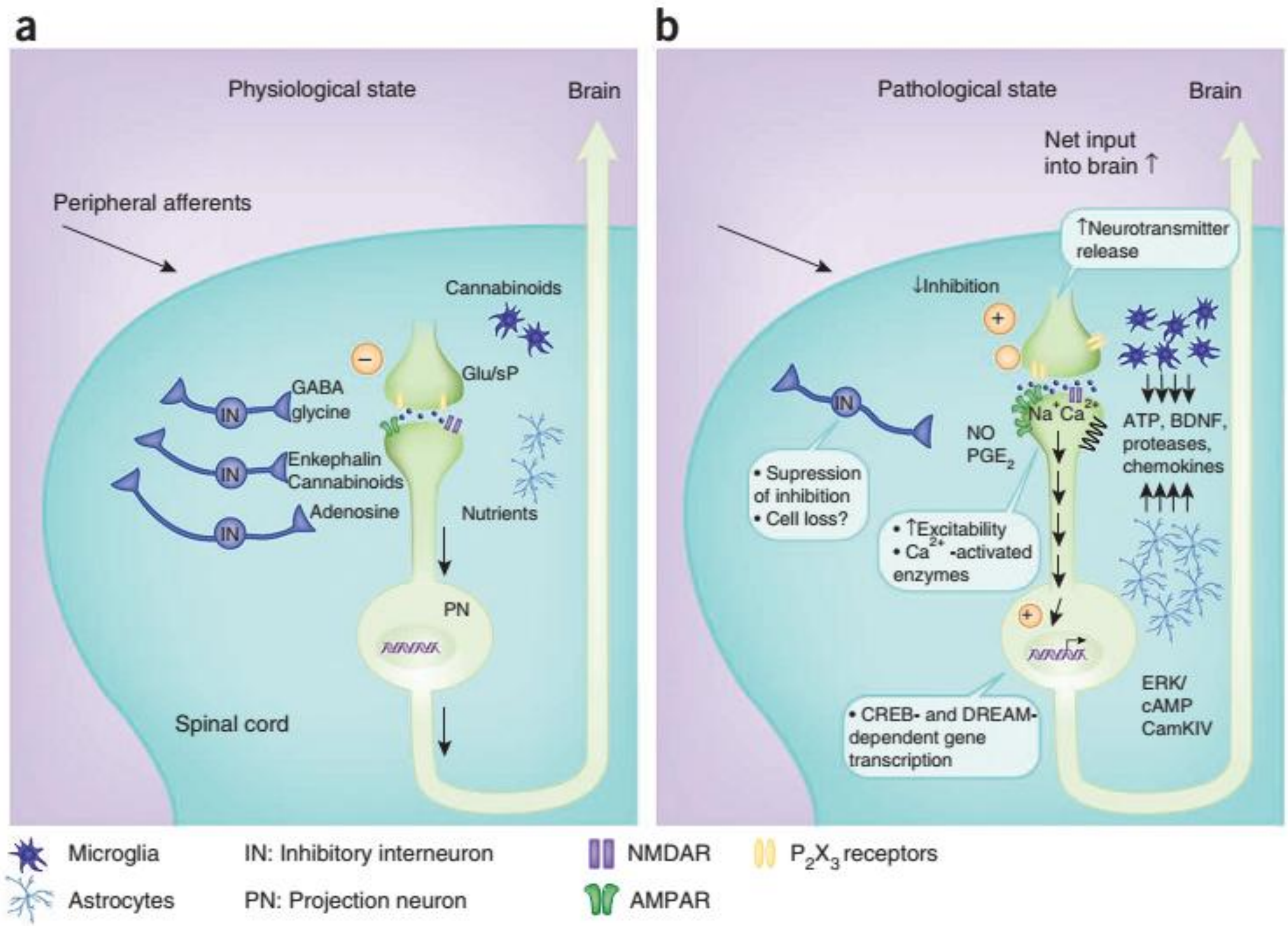
2008 - The International Association for the Study of Pain (IASP)



b New definitions



MECHANISM OF HYPERALGESIA



Nat Med. 2010 Nov;16(11):1258-66.

DEFINITION

Opioid-induced hyperalgesia (OIH) is the increased sensitivity to pain caused by exposure to opioids.

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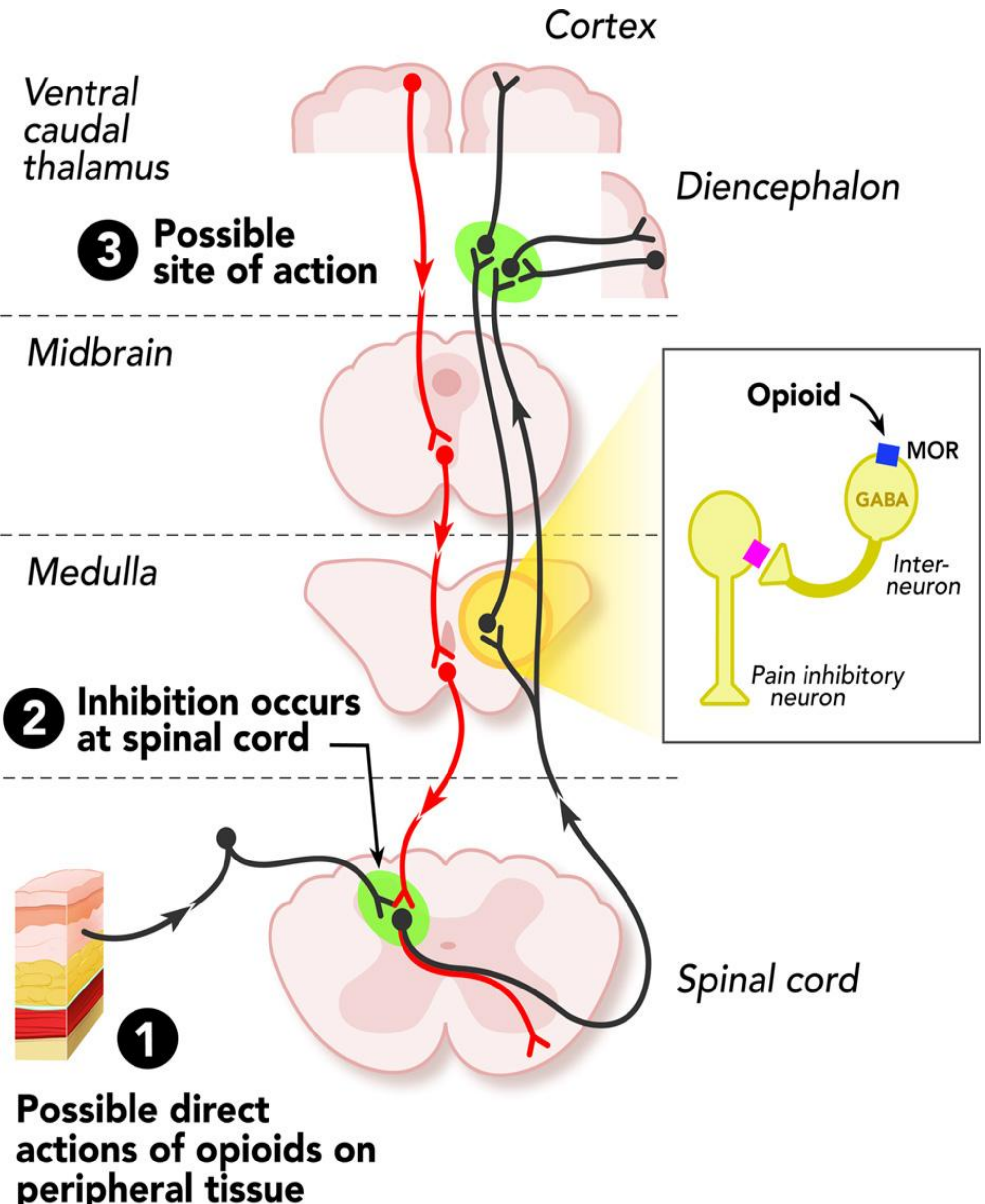
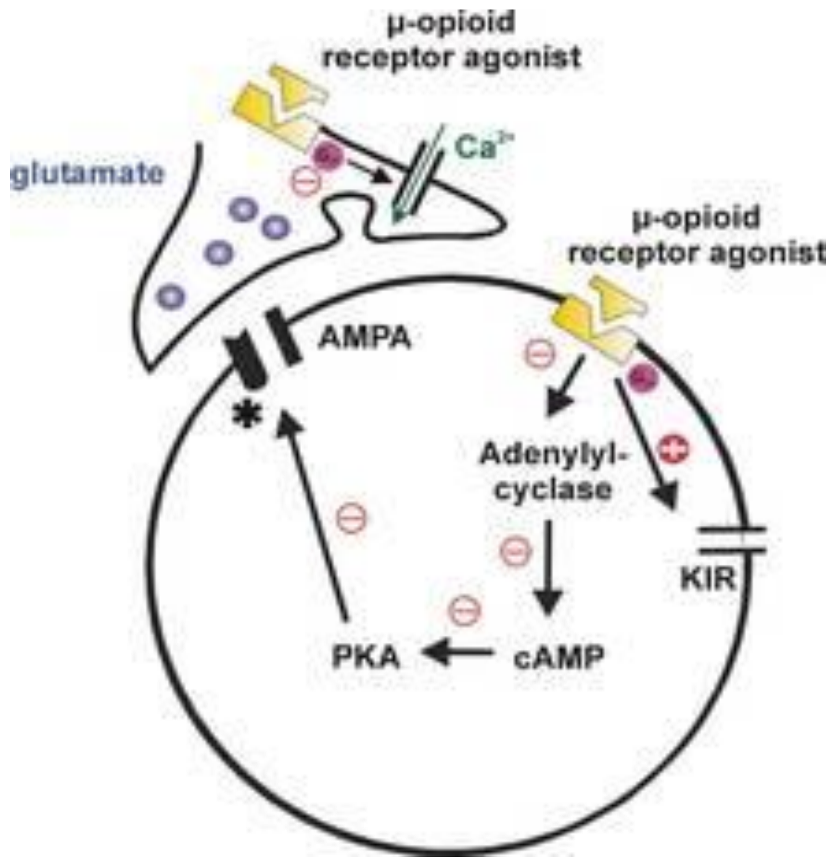
Lancet Neurol. 2014 Sep;13(9):924-35

Mechanism of OIH is still unclear but supposed multifactorial.

Mechanism of action





MECHANISM OF OIH

1. **NMDA –receptor activation**: opioids possess agonistic effect on the NMDA receptors in the spinal cord
2. **Spinal dynorphin**: endogenous opioid –activate the kappa opioid receptor and to NMDA receptor => spinal excitatory neuropeptides
3. **Descending facilitation**: chronic morphine exposure increases the number of the On-cells and promotes pain sensation via enhanced sensitization of the On-cells to painful stimuli
4. **Decreased reuptake of nociceptive neurotransmitters** such as substance P and glutamate from the afferent fibers in the spinal cord and the increased responsiveness of the spinal neurons to such transmitters after chronic opioid intake

Youssef, et al., J Pain Relief 2015, 4:3

ANESTHESIOLOGY
The Journal of the American Society of Anesthesiologists, Inc.

From: Opioid-induced Hyperalgesia:A Qualitative Systematic Review

Anesthes. 2006;104(3):570-587.

Table 3. Animal Studies Reporting Opioid-induced Hyperalgesia during Maintenance and Withdrawal

Investigator(s), yr	Reference	Animal	Route	Drug	Nociceptive Test	Mechanism(s) Explored
Aley and Levine, 1995	50	Rat	ID	DAMGO	Mechanical	
Aley and Levine, 1997	51	Rat	ID	DAMGO	Mechanical	AC, calcium, PKC
Aley and Levine, 1997	52	Rat	ID	DAMGO	Mechanical	PKC
Aley and Levine, 1997	53	Rat	ID	DAMGO	Mechanical	
Arts *et al.*, 1991	54	Mouse	ICV	Morphine	Thermal	Dynorphin
Bederson *et al.*, 1990	142	Rat	IV	Morphine	Thermal	RVM (on cell/off cell activity)
Bie *et al.*, 2003	143	Rat	IV	Morphine	Thermal	NRM (α1-adrenergic receptor)
Bie, 2003	144	Rat	IP	Morphine	Thermal	NRM (κ-opioid receptor)
Burdin *et al.*, 1992	145	Rat	PAG	Morphine	Electrical	PAG (opioid modulation)
Celerier *et al.*, 1999	38	Rat	SC	Morphine Fentanyl	Mechanical	NMDA receptor
Celerier *et al.*, 2000	43	Rat	SC	Fentanyl	Mechanical	NMDA receptor
Celerier *et al.*, 2001	37	Rat	SC	Heroin	Mechanical	NMDA receptor
Celerier *et al.*, 2004	39	Mouse	SC	Fentanyl	Mechanical Chemical	PKCγ
Christensen and Kayser, 2000	146	Rat	SC	Morphine	Mechanical	
Colpaert *et al.*, 2002	147	Rat	SC	Morphine	Mechanical	
Crain and Shen, 2004	136	Rat	SC	Morphine	Thermal	Neuraminidase/GM1 ganglioside
Davies *et al.*, 2003	49	Mouse	SC	Morphine	Mechanical	
Doerr and Kristal, 1991	148	Rat	IP	Morphine	Thermal	Amniotic fluid
Dunbar and Pulai, 1998	60	Rat	IT	Morphine	Thermal	NMDA receptor
Dunbar *et al.*, 2000	65	Rat	IT	Morphine	Thermal	Cyclooxygenase
Dunbar and Karamian, 2003	100	Rat	IT	Morphine	Thermal	EAA release, NMDA receptor
Ekblom *et al.*, 1993	149	Rat	IV	Morphine	Thermal	
Galeotti *et al.*, 2002	150	Mouse	Oral	Morphine	Thermal	Caffeine, indomethacin, prochlorperazine
Gardell *et al.*, 2002	76	Rat	SC	Morphine	Mechanical Thermal	Dynorphin
Grilly *et al.*, 1981	151	Rat	SC	Morphine	Electrical	
Grilly *et al.*, 1986	152	Rat	SC	Morphine	Electrical	
Harris *et al.*, 2004	153	Rat	IP	Morphine	Thermal	
Heinzen and Pollack, 2004	154	Rat	IV	Morphine	Electrical	NOS
Hendrie, 1985	137	Rat	Oral	Morphine	Thermal	Adrenocorticotropin
Hendrie, 1989	155	Mouse	IP	Morphine	Thermal	Endogenous opioid system
Hoffmann *et al.*, 1998	156	Rat	SC	Morphine	Thermal	Genetic factors
Ibuki *et al.*, 1997	45	Rat	IT	Morphine	Thermal	NMDA receptor, EAA
Johnston *et al.*, 2004	66	Rat	IT	Morphine	Thermal	Cytokines
Kang *et al.*, 2002	157	Rat		Fentanyl	Thermal Mechanical	Cyclooxygenase activity
Kaplan and Fields, 1991	158	Rat	RVM, IV	Morphine	Thermal	RVM
Kayan and Mitchell, 1968	159	Cat	SC	Morphine	Electrical	
Kayan *et al.*, 1971	32	Rat	SC	Morphine	Thermal	
Kest *et al.*, 2002	160	Mouse	SC	Morphine	Thermal	Genetic factors
Khasar *et al.*, 1995	55	Rat	ID	DAMGO	Thermal	AC
Kim *et al.*, 1990	161	Rat	IV	Morphine	Thermal	
Kim and Siegel, 2001	162	Rat	IV	Morphine	Thermal	Cholecystokinin
Kissin *et al.*, 2000	163	Rat	IV	Alfentanil	Mechanical	NMDA receptor
Lane *et al.*, 2004	164	Rat	PAG	Morphine	Thermal	PAG
Larcher *et al.*, 1998	165	Rat	SC	Heroin	Mechanical	NMDA receptor
Laulin *et al.*, 1999	40	Rat	SC	Heroin	Mechanical	NMDA receptor
Laulin *et al.*, 2002	42	Rat	SC	Fentanyl	Mechanical	NMDA receptor
Li *et al.*, 2001	36	Rat	SC	Morphine	Thermal, mechanical, incision	Endogenous opioid system
Li *et al.*, 2001	46	Mouse	SC	Morphine Fentanyl	Thermal, mechanical, chemical	NMDA, NOS and HO receptors
Li and Clark, 2002	35	Mouse	SC	Morphine	Thermal, mechanical, IT neurotransmitters	Glutamate, substance P
Liang *et al.*, 2003	73	Mouse	SC	Morphine	Thermal, mechanical	HO system
Manning *et al.*, 1996	166	Rat	SC	Morphine	Thermal	NMDA receptor
Mao *et al.*, 1994	48	Rat	IT	Morphine	Thermal	NMDA receptor, non-NMDA glutamate receptor, PKC

(continued)

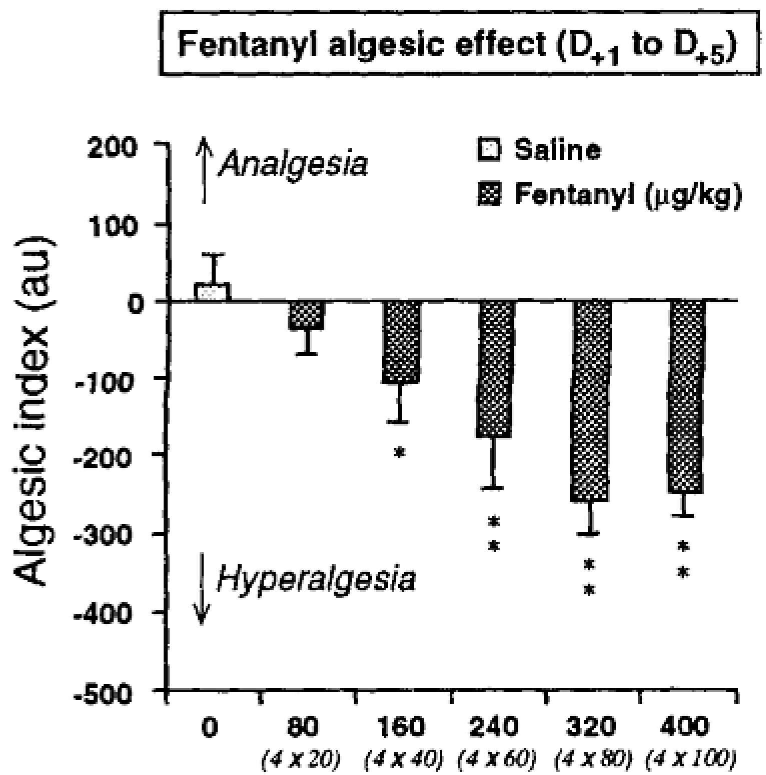
Date of download: 5/7/2017

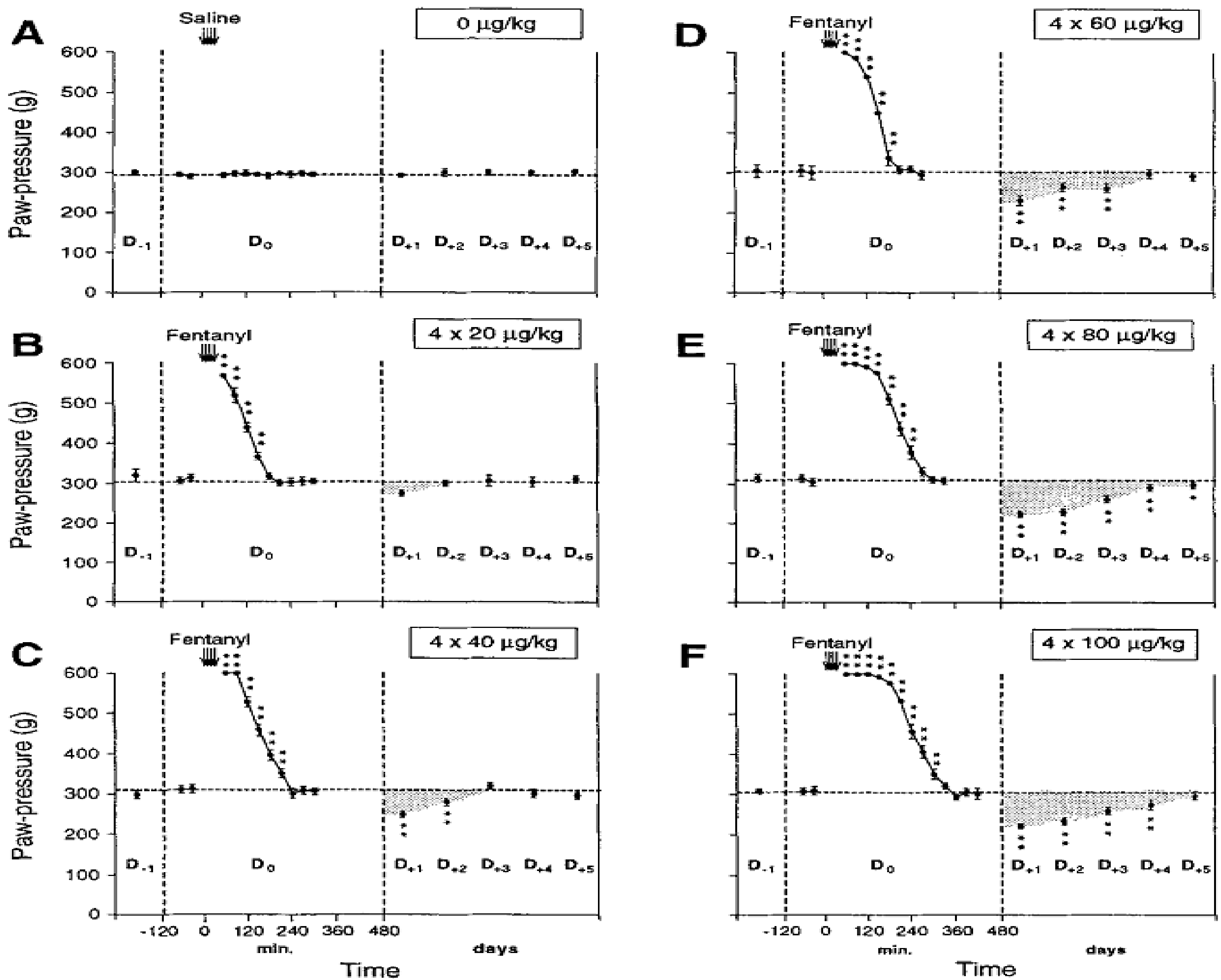
Anesthesiology
2000; 92:465–72

Long-lasting Hyperalgesia Induced by Fentanyl in Rats

Preventive Effect of Ketamine

Evelyne Célèrier, Ph.D., Cyril Rivat, B.S.,* Yan Jun, M.D.,† Jean-Paul Laulin, Ph.D.,‡ Agnès Larcher, Ph.D.,§ Patrick Reynier, M.D.,‖ Guy Simonnet, Ph.D.#*





A
Saline
0 µg/kg
B
Fentanyl
4 x 20 µg/kg
C
Fentanyl
4 x 40 µg/kg
D
Fentanyl
4 x 60 µg/kg
E
Fentanyl
4 x 80 µg/kg
F
Fentanyl
4 x 100 µg/kg
Paw-pressure (g)
0
100
200
300
400
500
600
D-1
D0
D+1
D+2
D+3
D+4
D+5
-120
0
120
240
360
480
min.
days
Time

Short-term infusion of the μ-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal

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Table 1
Heat pain (visual analog pain intensity scale; 0–100 mm)

Drug[a]				
Infusion 1	Placebo	Placebo	S-Ketamine	S-Ketamine
Infusion 2	Placebo	Remifentanil	Placebo	Remifentanil
Time[b]				
−20 min (before infusion)	47 ± 5	49 ± 11	45 ± 11	49 ± 10
15 min (infusion 1)	45 ± 6	50 ± 12	27 ± 16*	36 ± 18*
65 min (infusion 1 and 2)	45 ± 5	25 ± 15*	25 ± 16*	12 ± 11*
105 min (infusion 1 and 2)	45 ± 6	27 ± 20*	26 ± 15*	14 ± 14*
155 min (infusion 1)	47 ± 6	42 ± 8	31 ± 15*	39 ± 15*

Values are mean ± SD. *Significant decrease in heat pain compared with saline placebo (two-way RM-ANOVA and Student–Newman–Keuls post hoc pairwise comparison; $P < 0.01$).

[a] Infusion 1 contained either S-ketamine or saline placebo, whereas infusion 2 contained either remifentanil or saline placebo. Infusion 1 started 35 min before infusion 2 and was continued for an additional 50 min after infusion 2 had been stopped.

[b] Times are given relative to the start of infusion 1.

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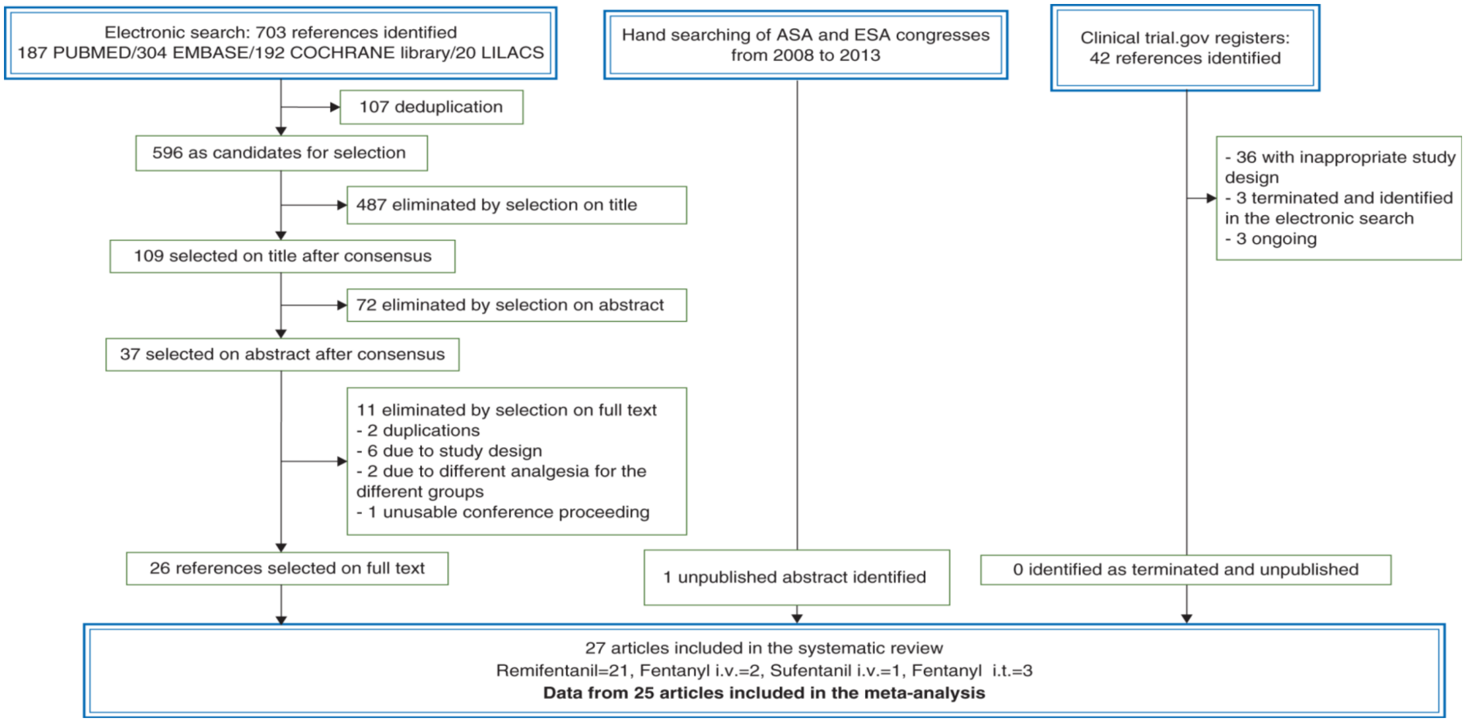
BJA

Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis

D. Fletcher[1,2,3]* and V. Martinez[1,2,3]



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Br J Anaesth. 2014;112(6):991-1004. doi:10.1093/bja/aeu137

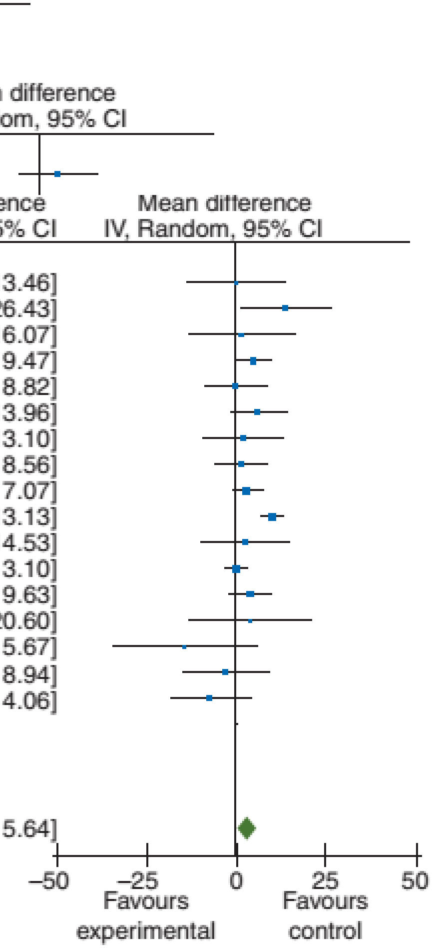
PAIN INTENSITY

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Pain at 1h								
Agata 2010	51.5	14.7	15	47.5	20.8	15	7.3%	4.00 [−8.89, 16.89]
Carvalho 2012	7.9	10	9	10.8	10	9	9.5%	−2.90 [−12.14, 6.34]
Cho 2008								
Cortinez 20(								
Guignard 20								
Lee 2013								
Lee 2013 a								
Ryu 2007								
Shin 2010								
Terao 2010								
Xuerong 20(								
Yeom 2012								
Total (95% (								
Heterogenei								
Test for over								

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Pain at 4h								
Agata 2010	46	18	15	40	17.3	15	5.6%	6.00 [−6.63, 18.63]
Carvalho 201								
Cho 2008								
Guignard 200								
Joly 2005								
Lee 2013								
Lee 2013 a								
Richebe 2011								
Ryu 2007								
Shin 2010								
Terao 2010								
Tversko 1994								
Xuerong 2008								
Total (95% CI								
Heterogeneity								
Test for overa								

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Pain at 24h								
Agata 2010	19.1	20.2	15	19.1	17.3	15	3.0%	0.00 [−13.46, 13.46]
Carvalho 2012	35	13.8	10	21.2	15	10	3.3%	13.80 [1.17, 26.43]
Cho 2008	21.4	22.6	20	20	24.7	20	2.6%	1.40 [−13.27, 16.07]
Cooper 2002	19.8	2.9	18	15.1	9.9	18	9.7%	4.70 [−0.07, 9.47]
Fechner 2012	23	14	16	23	12	18	5.5%	0.00 [−8.82, 8.82]
Guignard 2000	46.1	13.5	24	39.9	14.2	25	6.4%	6.20 [−1.56, 13.96]
Joly 2005	31.5	22.1	25	29.5	17.7	25	4.0%	2.00 [−9.10, 13.10]
Lahtinen 2008	30.6	20.1	45	29.1	13.4	45	7.0%	1.50 [−5.56, 8.56]
Lee 2013	22.8	7.5	29	19.6	7.4	28	10.9%	3.20 [−0.67, 7.07]
Lee 2013 a	23.8	6.8	29	13.7	4.9	30	12.0%	10.10 [7.07, 13.13]
Richebe 2011	18.7	16.8	19	16.3	21.1	19	3.5%	2.40 [−9.73, 14.53]
Ryu 2007	28.8	6.2	30	28.6	5.2	30	12.2%	0.20 [−2.70, 3.10]
Shin 2010	34.75	24.27	88	30.78	12.66	98	8.6%	3.97 [−1.69, 9.63]
Terao 2010	29	16	13	25	26	13	2.1%	4.00 [−12.60, 20.60]
Tversko 1994	23.3	22	9	37.5	21	9	1.6%	−14.20 [−34.07, 5.67]
Xuerong 2008	6	14	15	9	19	15	3.6%	−3.00 [−14.94, 8.94]
Yeom 2012	39	14	20	46	21	20	4.0%	−7.00 [−18.06, 4.06]
Total (95% CI)			425			438	100.0%	3.01 [0.39, 5.64]

Heterogeneity: τ^2=12.56; χ^2=35.25, df=16 (P=0.004); I^2=55%
Test for overall effect: Z=2.25 (P=0.02)



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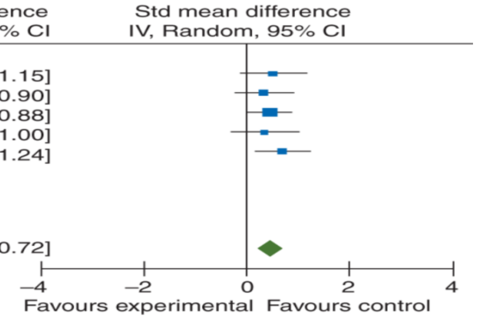
MORPHINE CONSUME 24HRS

Study or subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std mean difference IV, Random, 95% CI
Morphine titration								
Cho 2008	2.4	0.8	20	1.95	0.9	20	14.4%	0.52 [−0.11, 1.15]
Joly 2005	20	7.3	25	16	14.5	25	18.4%	0.34 [−0.22, 0.90]
Lahtinen 2008	4	3.5	45	2	5	45	32.8%	0.46 [0.04, 0.88]
Richebe 2011	12	5	19	10	6	19	14.0%	0.35 [−0.29, 1.00]
Tirault 2006	0.2	0.13	30	0.11	0.12	28	20.3%	0.71 [0.18, 1.24]
Total (95% CI)			139			137	100.0%	0.48 [0.24, 0.72]

Heterogeneity: $\tau^2=0.00$; $\chi^2=1.11$, df=4 ($P=0.89$); $I^2=0\%$

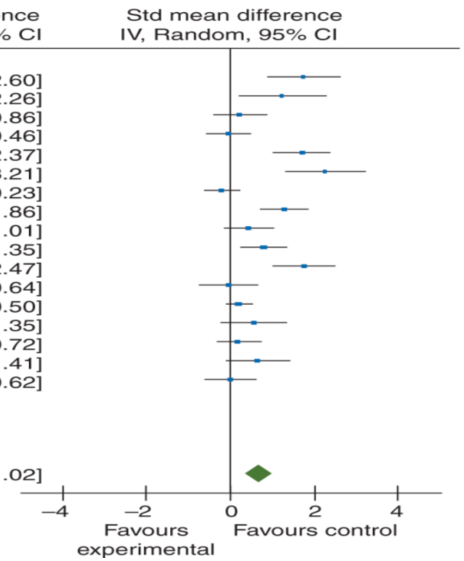
Test for overall effect: $Z=3.94$ ($P<0.0001$)



Study or subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std mean difference IV, Random, 95% CI
Morphine consumption at 24 h								
Agata 2010	1.48	0.41	15	0.64	0.52	15	5.0%	1.75 [0.89, 2.60]
Carvalho 2012	24	7.1	9	10.72	12.7	9	4.4%	1.23 [0.20, 2.26]
Cho 2008	33.9	17.5	20	30.4	10.9	20	6.0%	0.24 [−0.39, 0.86]
Cortinez 2001	28	14.2	30	28.6	12.4	30	6.5%	−0.04 [−0.55, 0.46]
Guignard 2000	57.6	13.5	24	38	8.6	25	5.8%	1.71 [1.05, 2.37]
Kim 2013	17.8	3.6	15	11.1	1.9	15	4.7%	2.26 [1.32, 3.21]
Lahtinen 2008	71.1	28.86	45	77.35	36.25	45	6.8%	−0.19 [−0.60, 0.23]
lee 2011	4.71	0.9	30	3.7	0.6	30	6.3%	1.30 [0.74, 1.86]
Lee 2011 a	64.8	1.8	25	64	1.7	25	6.3%	0.45 [−0.11, 1.01]
Lee 2013	60	2.3	29	58	2.6	28	6.3%	0.80 [0.26, 1.35]
Lee 2013 a	51.4	4.2	16	41.4	6.2	30	5.6%	1.76 [1.04, 2.47]
Sahin 2004	17.26	11.87	16	17.9	12.2	16	5.7%	−0.05 [−0.74, 0.64]
Shin 2010	34.7	24	88	30.78	12.6	98	7.2%	0.21 [−0.08, 0.50]
Terao 2010	0.91	0.4	13	0.7	0.32	13	5.3%	0.56 [−0.22, 1.35]
Tirault 2006	0.42	0.26	27	0.34	0.48	30	6.4%	0.20 [−0.32, 0.72]
Xuerong 2008	26.9	12.8	15	19.5	8.3	15	5.5%	0.67 [−0.07, 1.41]
Yeom 2012	0.06	0.02	20	0.06	0.02	20	6.0%	0.00 [−0.62, 0.62]
Total (95% CI)			437			464	100.0%	0.70 [0.37, 1.02]

Heterogeneity: $\tau^2=0.36$; $\chi^2=83.48$, df=16 ($P<0.00001$); $I^2=81\%$

Test for overall effect: $Z=4.18$ ($P<0.0001$)



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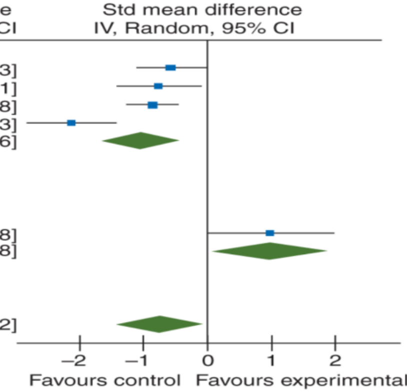
PRIMARY AND SECONDARY HYPERALGESIA

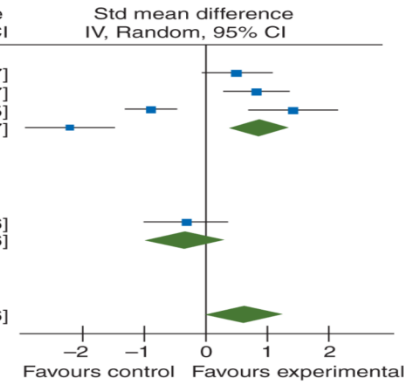
A

Study or subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std mean difference IV, Random, 95% CI
Remifentanil								
Song 2011	682	891	28	1,352	1,383	28	21.3%	−0.57 [−1.10, −0.03]
Richebe 2011	138.6	40.7	19	166.7	30.3	19	20.0%	−0.77 [−1.43, −0.11]
Lee 2013	89	37	29	129	47	280	22.6%	−0.86 [−1.25, −0.48]
Joly 2005	109.3	11.6	25	132.4	9.6	25	19.6%	−2.14 [−2.84, −1.43]
Subtotal (95% CI)			101			352	83.6%	−1.05 [−1.63, −0.46]
Heterogeneity: τ^2=0.27; χ^2=13.29, df=3 (P=0.004); I^2=77%								
Test for overall effect: Z=3.51 (P=0.0004)								
Fentanyl								
Tversko 1994	1.07	0.6	9	0.58	0.3	9	16.4%	0.98 [−0.01, −1.98]
Subtotal (95% CI)			9			9	16.4%	0.98 [−0.01, −1.98]
Heterogeneity: Not applicable								
Test for overall effect: Z=1.94 (P=0.05)								
Total (95% CI)			110			361	100.0%	−0.73 [−1.43, −0.02]
Heterogeneity: τ^2=0.54; χ^2=26.97, df=4 (P<0.0001); I^2=85%								
Test for overall effect: Z=2.01 (P=0.04)								
Test for subgroup differences: χ^2=11.94, df=1 (P=0.0005); I^2=91.6%								



B

Study or subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std mean difference IV, Random, 95% CI
Remifentanil								
Joly 2005	11.1	8	25	7.7	4.8	25	26.1%	0.51 [−0.06, 1.07]
Lee 2013 a	13.4	6.2	29	8.6	5.1	30	26.7%	0.84 [0.30, 1.37]
Richebe 2011	6.4	2.2	19	3.7	1.4	19	23.2%	1.43 [0.71, 2.15]
Subtotal (95% CI)			73			74	76.0%	0.88 [0.40, 1.37]
Heterogeneity: τ^2=0.09; χ^2=3.94, df=2 (P=0.14); I^2=49%								
Test for overall effect: Z=3.56 (P=0.0004)								
Sufentanil								
Fechner 2012	3.8	2	16	4.5	2.3	18	24.0%	−0.32 [−0.99, 0.36]
Subtotal (95% CI)			16			18	24.0%	−0.32 [−0.99, 0.36]
Heterogeneity: Not applicable								
Test for overall effect: Z=0.91 (P=0.36)								
Total (95% CI)			89			92	100.0%	0.61 [−0.03, 1.26]
Heterogeneity: τ^2=0.33; χ^2=12.98, df=3 (P=0.005); I^2=77%								
Test for overall effect: Z=1.87 (P=0.06)								
Test for subgroup differences: χ^2=7.91, df=1 (P=0.005); I^2=87.4%								



From: Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis

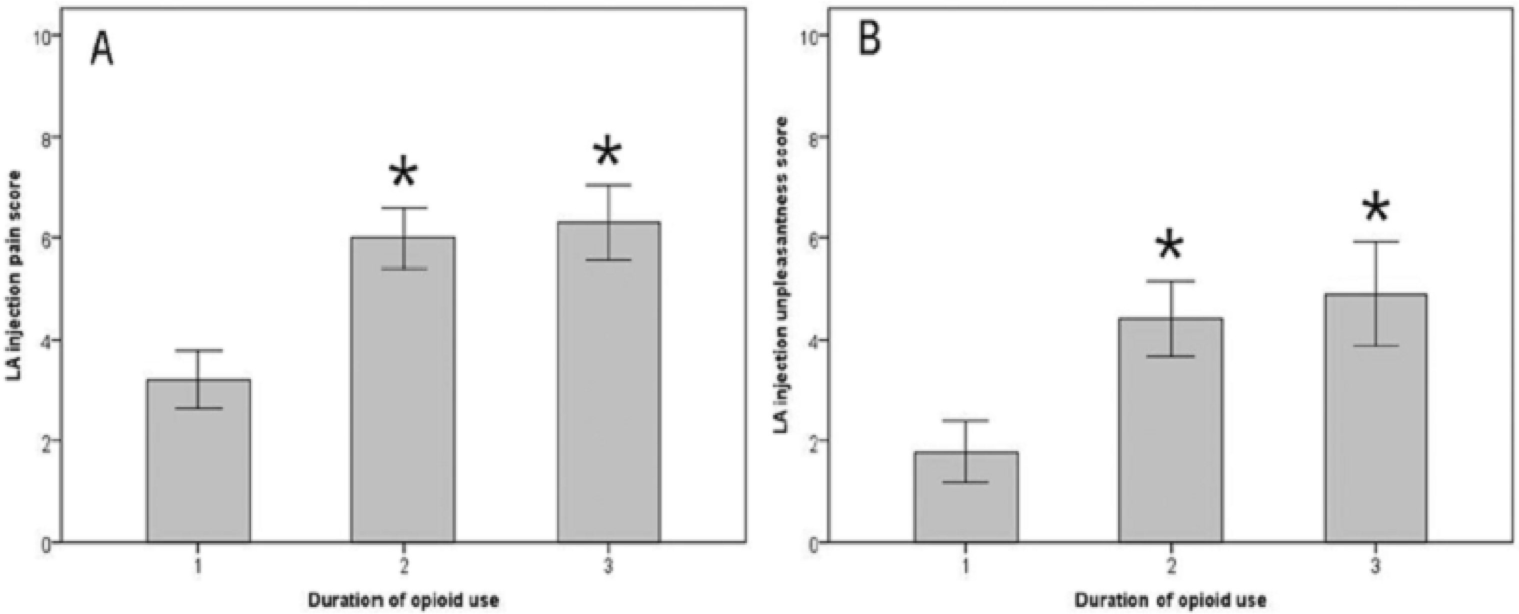
Br J Anaesth. 2014;112(6):991-1004. doi:10.1093/bja/aeu137

Prospective Study

High-Dose Daily Opioid Administration and Poor Functional Status Intensify Local Anesthetic Injection Pain in Cancer Patients

Shin Hyung Kim, MD, Duck Mi Yoon, MD, PhD, Kwan Woong Choi, MD, and Kyung Bong Yoon, MD, PhD

Pain Physician 2013; 16:E247-E256



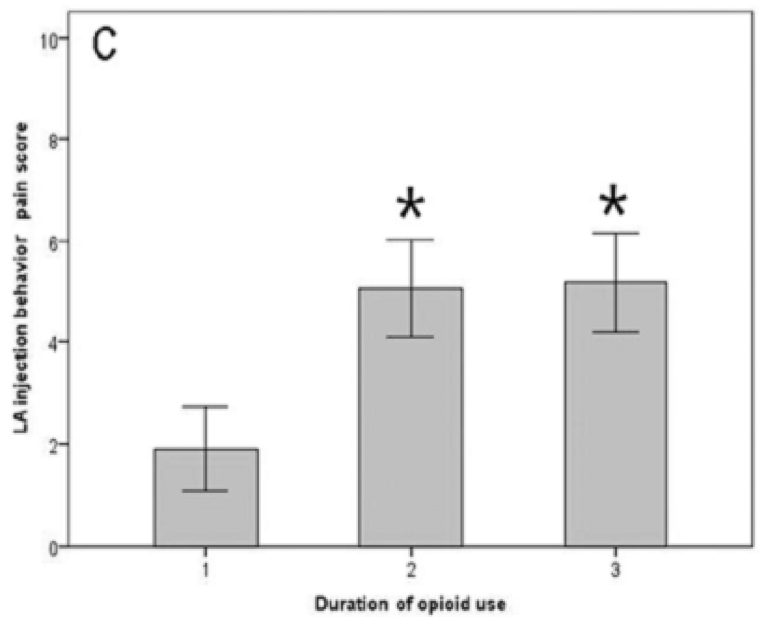
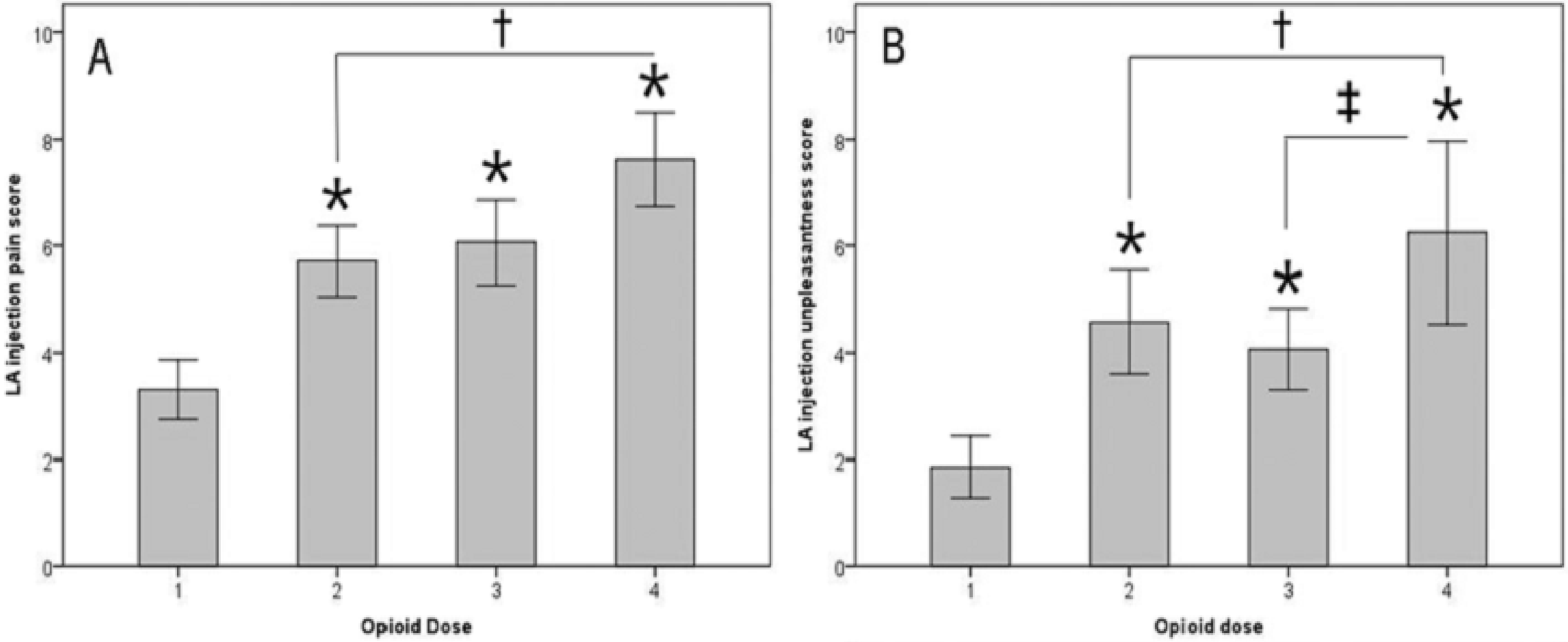


Fig. 3. *Standardized LA injection-specific pain (A), unpleasantness (B), and behavior pain score (C) as a function of opioid use duration. 1 = no opioids; 2 = ≤1 year; 3 =≥1 year. Error bars show 95 % confidence intervals. * P < 0.01 compared with group 1 (non-opioid group).*



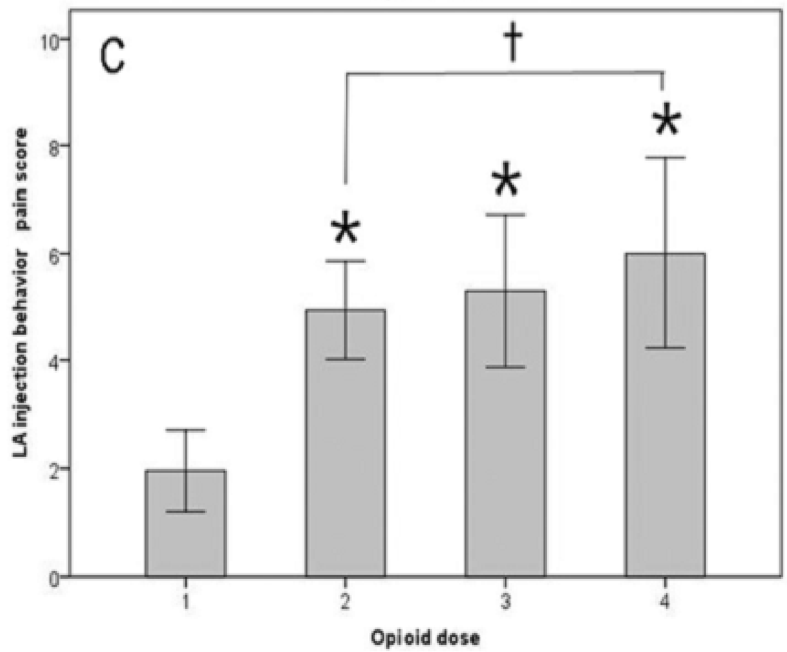


Fig. 2. *Standardized LA injection-specific pain (A), unpleasantness (B), and behavior pain score (C) as a function of the opioid dose. Doses are given in daily oral morphine equivalents: 1= no opioids; 2=1 to 59 mg (low); 3 = 60 to 199mg (intermediate); 4= ≥200mg (high). Error bars show 95 % confidence intervals. * P < 0.01 compared with group 1 (non-opioid group). †P < 0.05 for group 2 (low dose) vs. group 4 (high dose). ‡ P < 0.05 for group 3 (intermediate dose) vs. group 4 (high dose).*

Table 4. *Comparison between non-hyperalgesic (<7 NRS) and hyperalgesic (≥7 NRS) patients in response to LA injection stimulus in the opioid group.*

	Non-hyperalgesia (n=39)	**Hyperalgesia (n=23)**	***P* value**
Duration of opioid use, months	10.1±11.0 (1 month-3 years)	16.4±17.4 (1 month-6 years)	0.155
<1 year, n	24	11	
≥1 year, n	15	12	
Daily opioid dose, mg	101.3±77.0 (10-300)	298.5±304.6 (20-1080)	0.004
Low (1 to 59 mg) , n	22	3	
Intermediate (60 to 199 mg) , n	14	7	
High (≥200 mg), n	3	13	

CONCLUSION

- Minimize usage of opioids
- Multimodal analgesia: role of regional anesthesia
- Prevent hyperalgesia: ketamin, gabapentin, dexmedetomidine, clonidine

THANK YOU