Mitä uutta ketamiinista?

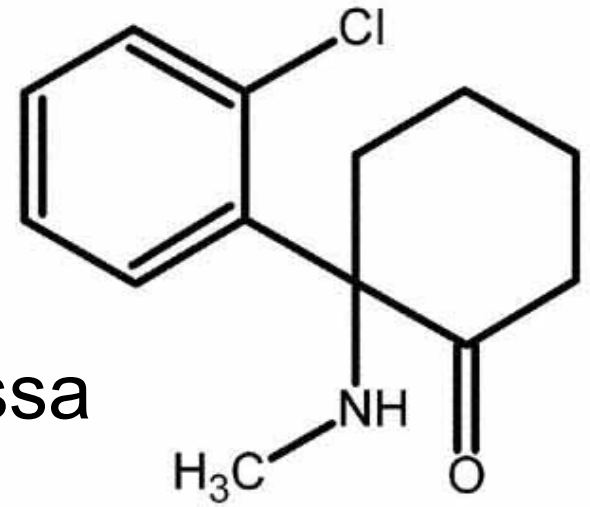
Anestesiakurssi

Helsinki, 28.3.2019

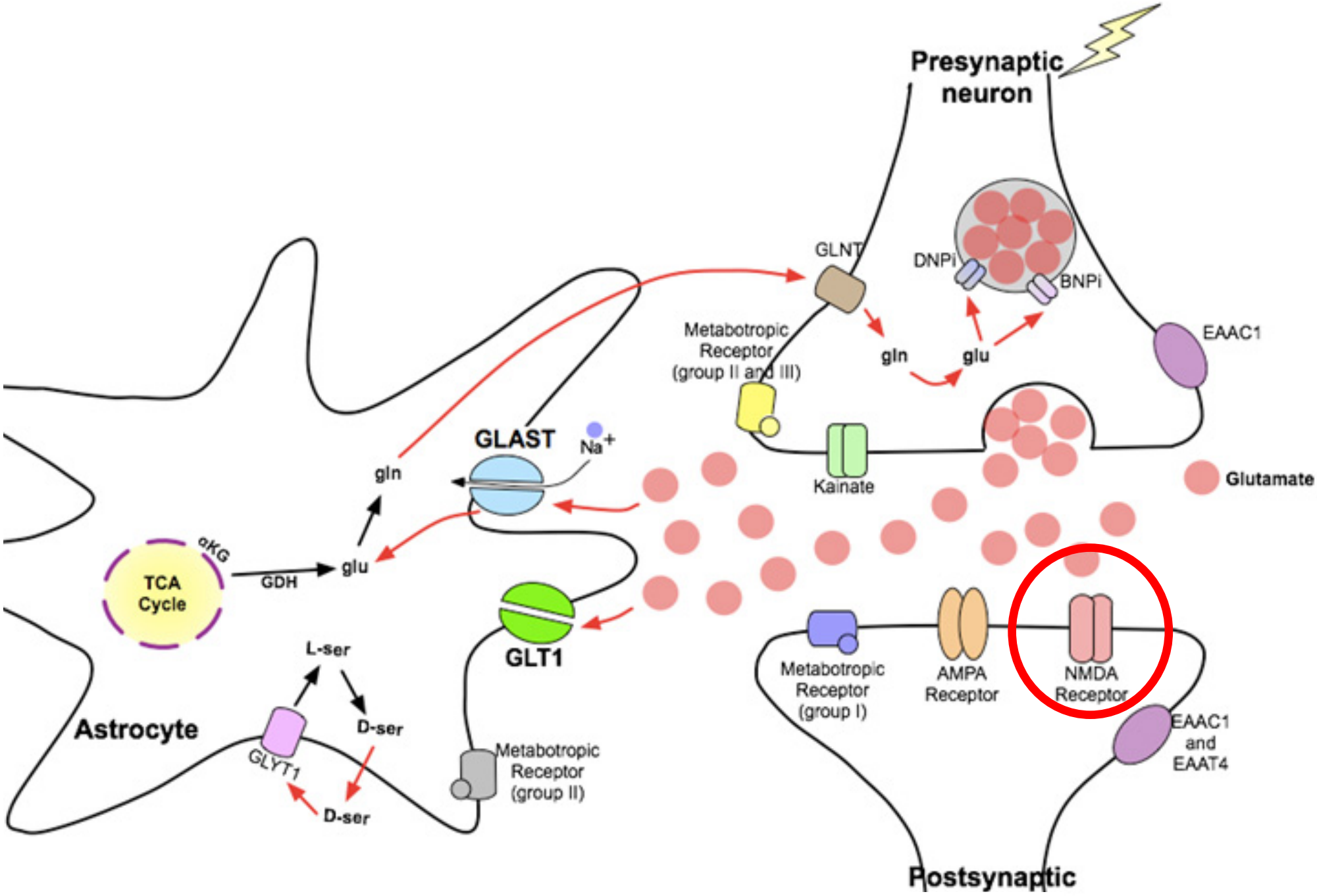
Teema V: Muuttuuko tuntemamme yleisanestesia?

Vesa Kontinen, dosentti, ylilääkäri
HYKS, Operatiivinen tulosyksikkö, ATeK
Jorvin sairaala, Leikkaus- ja anestesiayksiköt

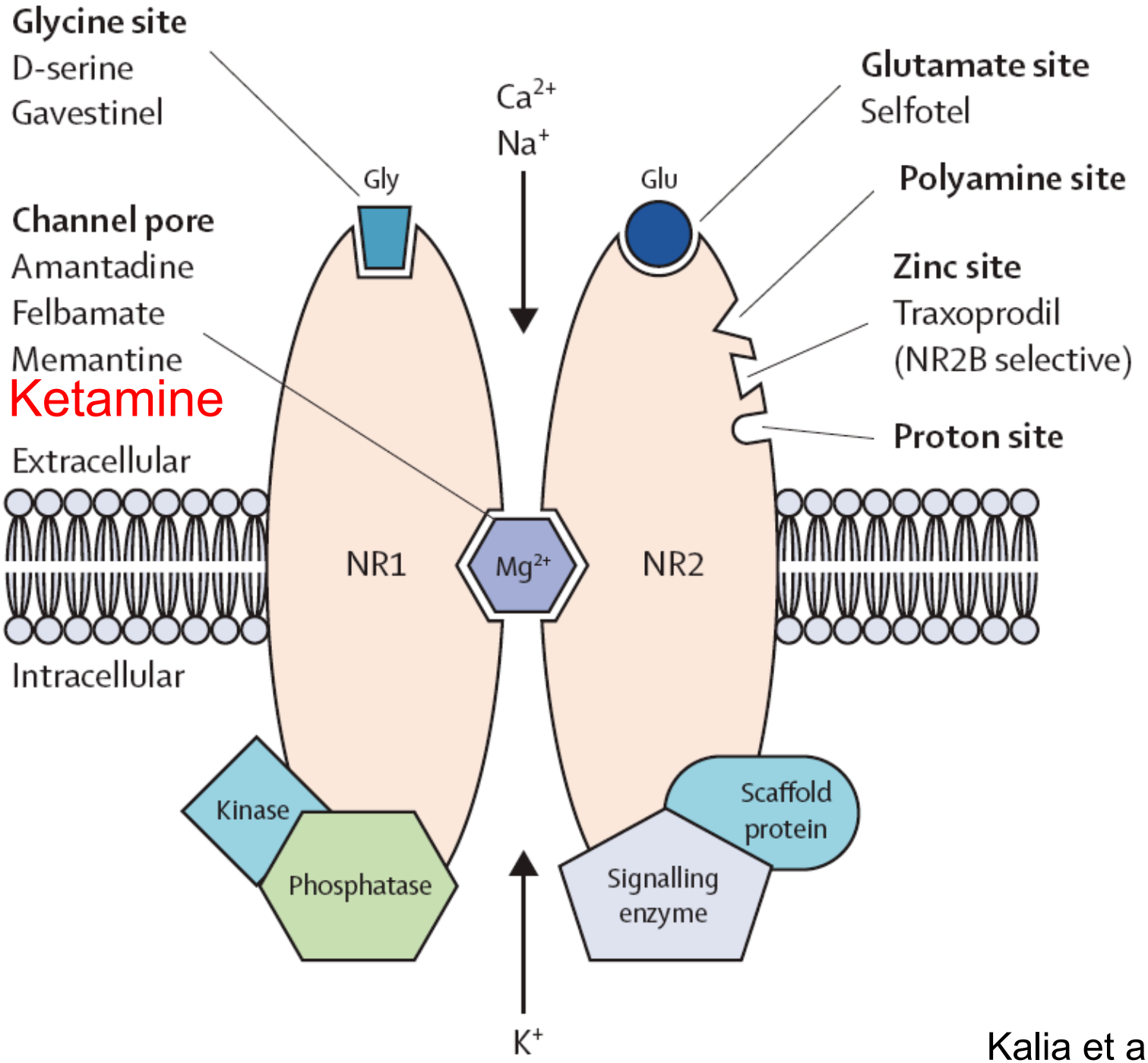
Ketamiinin käyttöalueita



- Anestesia, sedaatio
- Analgesia
  - adjuvanttina akuutissa kivussa
  - adjuvanttina syöpäkivussa
  - CRPS:n hoito?
  - muun kroonisen kivun hoito??
- Depression hoito



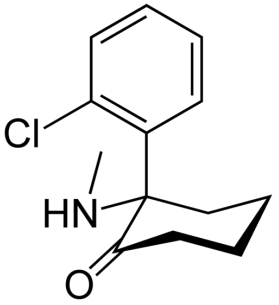
Liu et al. 2008

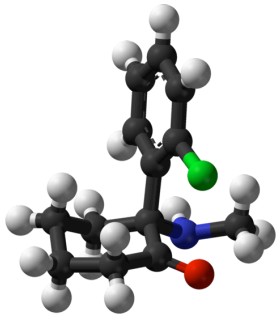


Kalia et al. 2008

Compound	[^{3}H]MK-801 binding	Electrophysiology in vitro	
	K_i values ± S.E.M. (μM)	IC_{50} (μM)	
		Cortex	Spinal cord
(*RS*)-Ketamine	0.53 ± 0.078		
(*R*)-Ketamine	1.4 ± 0.1	3.0 (1.4)	14 (1.4)
(*S*)-Ketamine	0.30 ± 0.013	0.9 (1.4)	4.0 (1.4)
(*RS*)-Norketamine	3.6 ± 0.49		
(*R*)-Norketamine	13 ± 1.8	39 (1.4)	75 (1.4)
(*S*)-Norketamine	1.7 ± 0.050	3.0 (0.8)	15 (1.4)
MK-801	0.0019 ± 0.0010	0.09 (1.0)	
PCP	0.060 ± 0.013	0.4 (0.9)	

Ebert et al. 1997





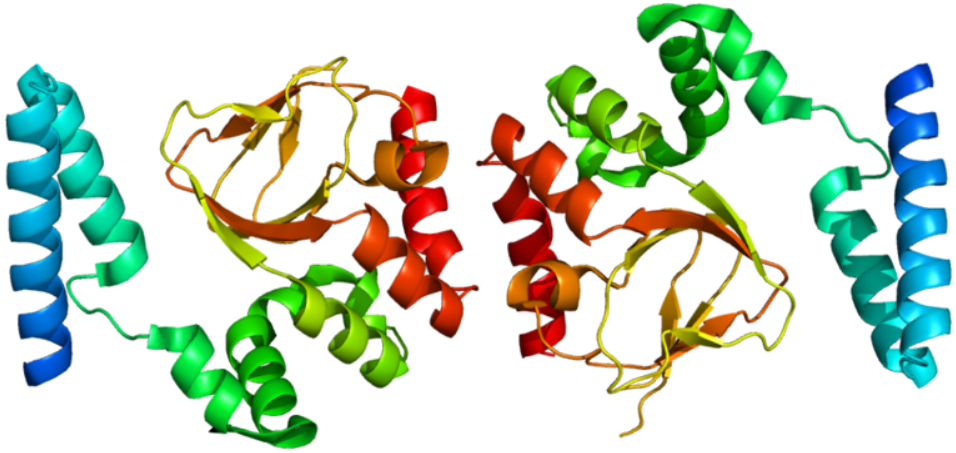
Receptor	K_i (µmol/L)	
	S-(+)-ketamine	*R*-(−)-ketamine
NMDA	0.9[a]	2.5[a]
Opioid µ	28.6[a]	83.8
Opioid κ	23.7[a]	60.0
Opioid δ	205.0	286.0
Opioid σ	131.0	19.0[a]
Muscarinic acetylcholine	125.0	91.0
Dopamine transporter	46.9[a]	390.0
Noradrenaline (norepinephrine) transporter	64.8	68.9
Serotonin transporter	156.0	148.0

a High affinity for the site.

K_i = inhibition constant.

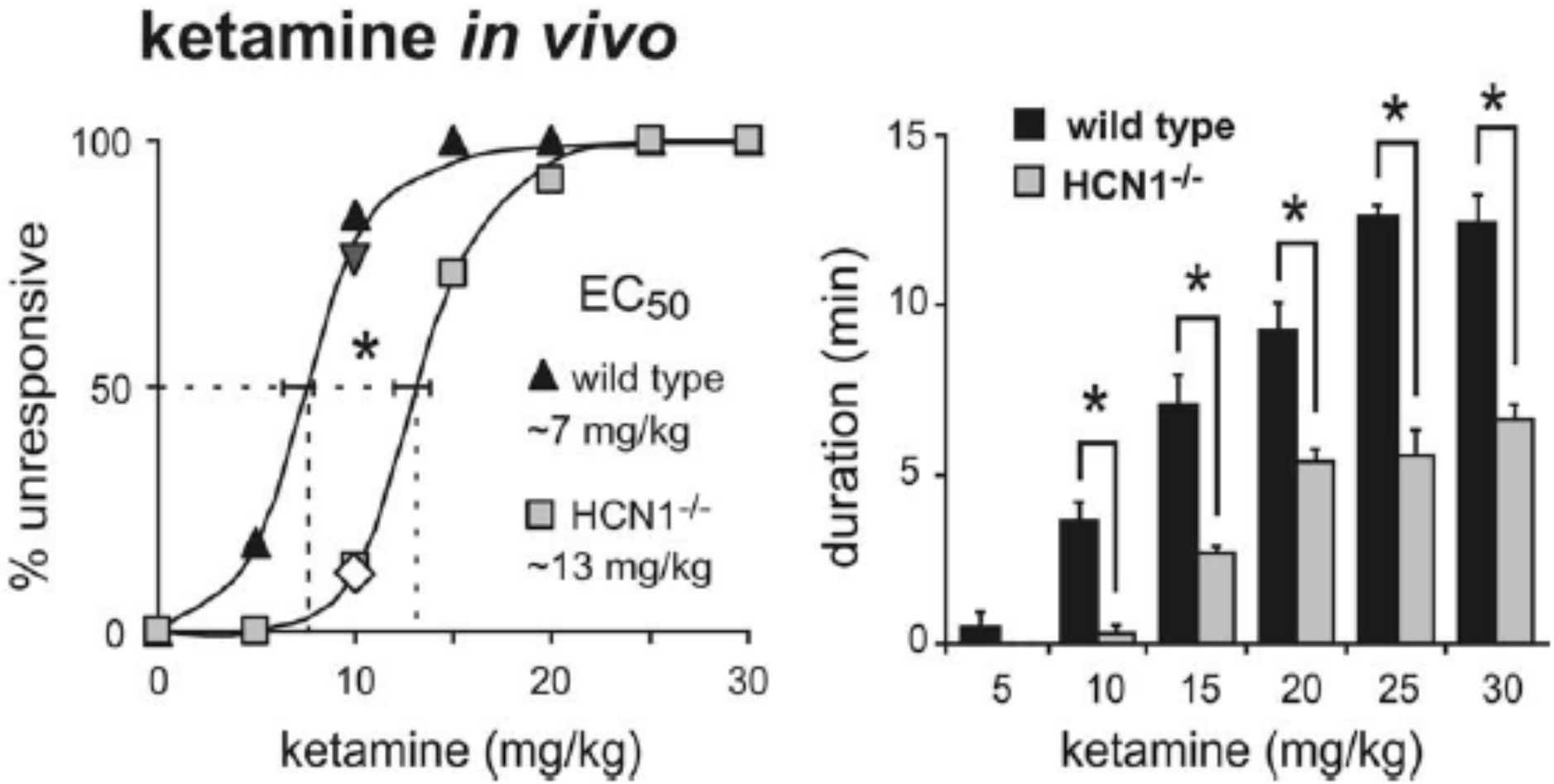
Nishimura & Sato 1999 (as cited in Wolff & Winstock 2006)

HCN1 ionikanava (hyperpolarization-activated cyclic nucleotide-gated channel 1)



- Na^+, K^+
- I_f “funny” sydänlihaksessa
- I_Q “queer” hippokampuksessa

- hyperpolarisaatio aktivoi, ei inaktivoidu
- depolarisoi neuronia hitaasti kohti tasapainopotentiaalia
- tärkeä neuronien tahdistuksessa



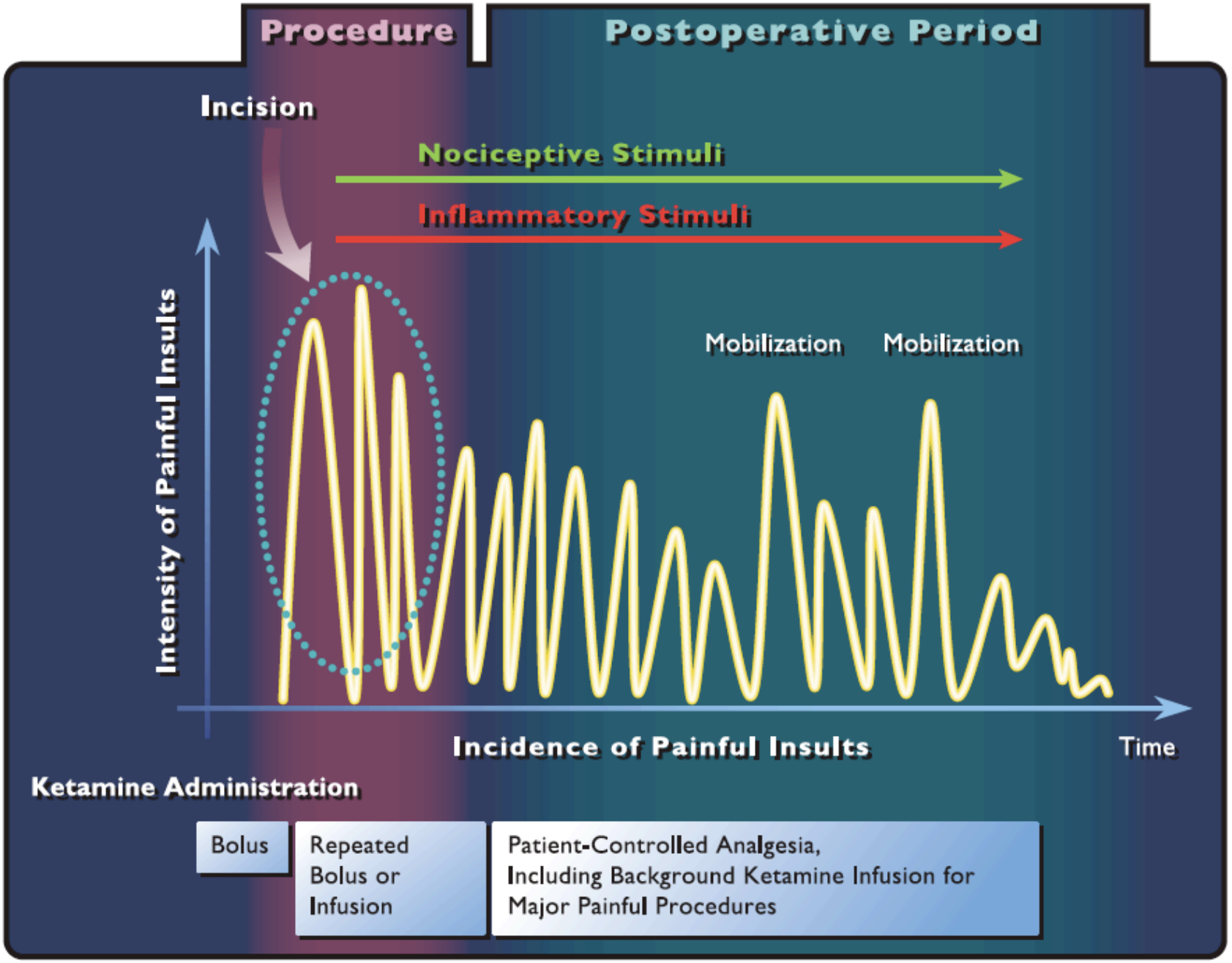
Chen et al. 2009

Ketamiinin mahdolliset hyödyt akuutin kivun hoidossa

- tehostunut kivunlievitys
- opioidin tarpeen väheneminen → opioidien haittavaikutusten väheneminen

- suora vaikutus opioidien aiheuttamiin haittoihin (esimerkiksi hyperalgesia)
- opioiditoleranssin väheneminen

- leikkauksen jälkeisen kivun kroonistumisen väheneminen?

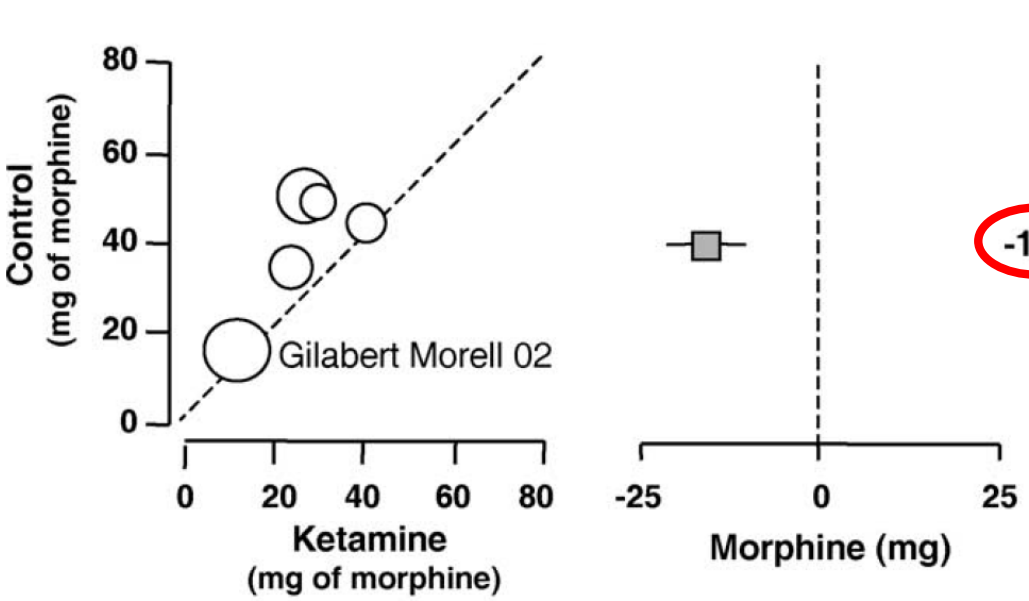


Himmelseher & Durieux 2005

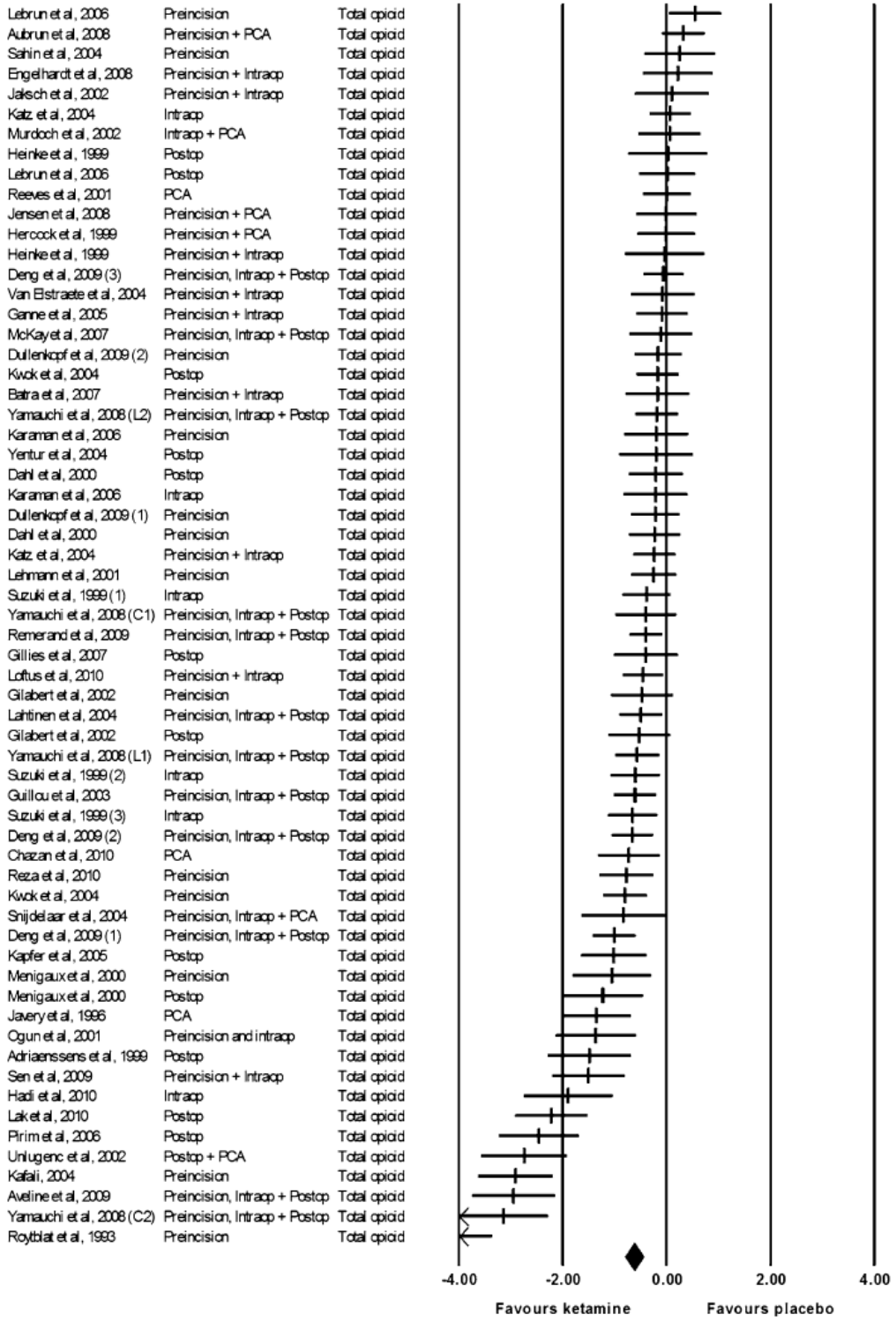
Review: Peri-operative ketamine for acute post-operative pain
Comparison: 01 Peri-operative ketamine vs control
Outcome: 01 Morphine (PCA) consumption over 24 h

Study or sub-category	n	Ketamine Mean (SD)	n	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Roytblat 1993	11	29.50 (7.50)	11	48.70 (13.00)		17.60	-19.20 [-28.07, -10.33]
Javery 1996	22	25.82 (16.40)	20	51.10 (20.80)		10.64	-25.28 [-36.68, -13.88]
Stubhaug 1997	10	64.50 (22.60)	10	68.00 (30.00)		2.55	-3.50 [-26.78, 19.78]
Ilkjær 1998	30	28.00 (21.00)	30	36.00 (23.00)		11.14	-8.00 [-19.14, 3.14]
Adriaenssens 1999	15	19.40 (10.70)	15	30.70 (15.90)		14.72	-11.30 [-21.00, -1.60]
Menigaux 2000 post	15	24.20 (17.80)	15	49.70 (24.10)		6.02	-25.50 [-40.66, -10.34]
Menigaux 2000 pre	15	28.20 (18.40)	15	49.70 (24.10)		5.88	-21.50 [-36.84, -6.16]
Guignard 2002	25	42.70 (16.30)	25	64.90 (27.00)		9.06	-22.20 [-34.56, -9.84]
Jaksch 2002	15	44.10 (45.23)	15	40.23 (17.16)		2.31	3.87 [-20.61, 28.35]
Guillou 2003	41	37.00 (24.00)	52	48.00 (22.00)		15.43	-11.00 [-20.47, -1.53]
Snijdelaar 2004	13	32.15 (18.59)	12	50.42 (24.70)		4.65	-18.27 [-35.52, -1.02]
Total (95% CI)	212		220			100.00	-15.98 [-19.70, -12.26]

Test for heterogeneity: $\chi^2 = 13.67$, df = 10 ($P = 0.19$), $I^2 = 26.8\%$
Test for overall effect: Z = 8.42 ($P < 0.00001$)

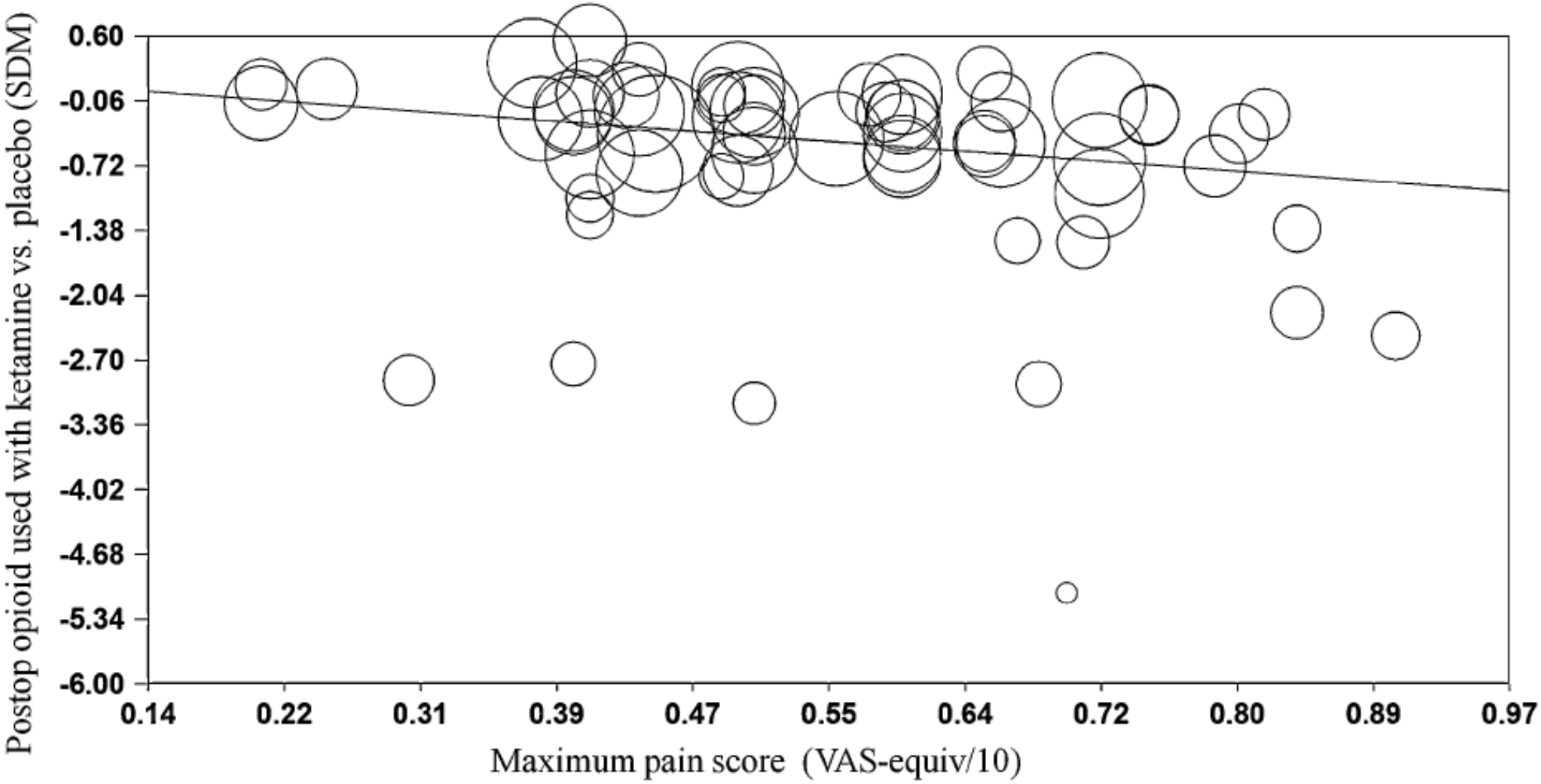


Bell et *al* 2005
Elia & Tramèr 2005
Subramaniam et *al* 2004



opioidin tarve:
-37 % [20-55%]

Laskowski et *al.* 2011



Laskowski et *al* 2011

Perioperative intravenous ketamine compared to placebo for acute postoperative pain: non-stratified analysis

Patient or population: adults undergoing any type of surgery
Settings: immediate postoperative period
Intervention: intravenous ketamine given before, during, or after surgery
Comparison: intravenous placebo

Outcomes	Details	Number of participants (studies)	Absolute values and effect of ketamine		Quality of th (GRADE)
			Measured values with placebo	Difference with perioperative intravenous ketamine (95% CI)	
Opioid consumption (mg morphine equivalents)	24 hours	4004 (65 RCTs)	Median 31 mg (mean 42 mg)	MD 7.6 mg lower (8.9 lower to 6.4 lower)	Moderate[1]

= opioidin tarve väheni 24% [21–29%]

Brinck et *al.* 2018

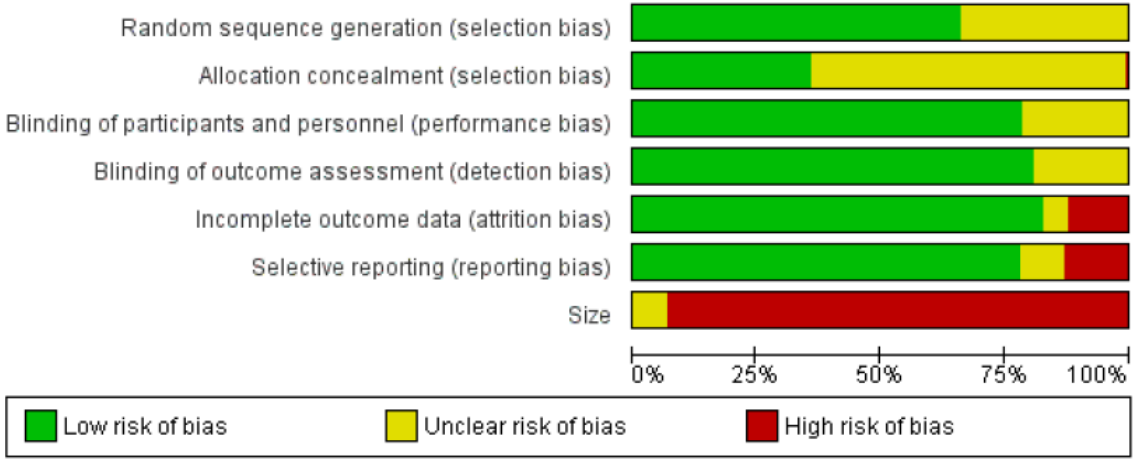
Surgery	Studies	Participants	Morphine equivalents (mg) MD (95% CI)	
Opioid consumption at 0-24 hours				
All studies	65	4004	−7.6 (−8.9 to −6.4)	24 %
Thoracotomy	4	421	−5.8 (−10.3 to −1.4)	21 %
Major orthopaedic	10	797	−19.7 (−28.6 to −10.2)	36 %
Major abdominal	16	1029	−10.3 (−13.8 to −6.8)	22 %
Total abdominal hysterectomy	9	511	−5.2 (−10.8 to 0.4)	19 %
Laparoscopic procedures	4	199	−2.7 (−6.2 to 0.8)	11 %

Brinck et *al.* 2018

Analysis	Studies	Participants	Participants (% of total)	VAS 0-100 (mm)
Pain at rest at 24 hours				
All studies	82	5004	100	−5 (−6.6 to −3.6)
Pain in control ≥ 40/100 mm	14	860	17	−17 (−25 to −9)

Brinck et *al.* 2018

Time to first request for analgesia/trigger of PCA (minutes)	All data (plus analysis omitting 1 highly aberrant study reporting time of over 1000 minutes)	1678 (31 RCTs)	Median 18 minutes (mean 39 minutes)	MD 54 minutes longer (37 to 71 longer) (MD 22 minutes longer omitting aberrant study (15 to 29 longer))	Moderate[4]
Hyperalgesia (cm^2)	As described, any time point	333 (7 RCTs)	Mean 15 cm^2	MD 7 cm^2 less (12 to 2 less)	Very low[5]
CNS adverse events	All events (major and minor), as described, any time point	6538 (105 RCTs)	52 per 1000	42 per 1000 RR 1.2 (0.95 to 1.4)	High[6]
Postoperative nausea and vomiting	All studies reporting outcomes, as described, any time point	5965 (95 RCTs)	271 per 1000	230 per 1000 RR 0.88 (0.81 to 0.96 Need to treat 24 people to prevent one episode of PONV (16 to 54)	High[6]



Brinck et *al.* 2018

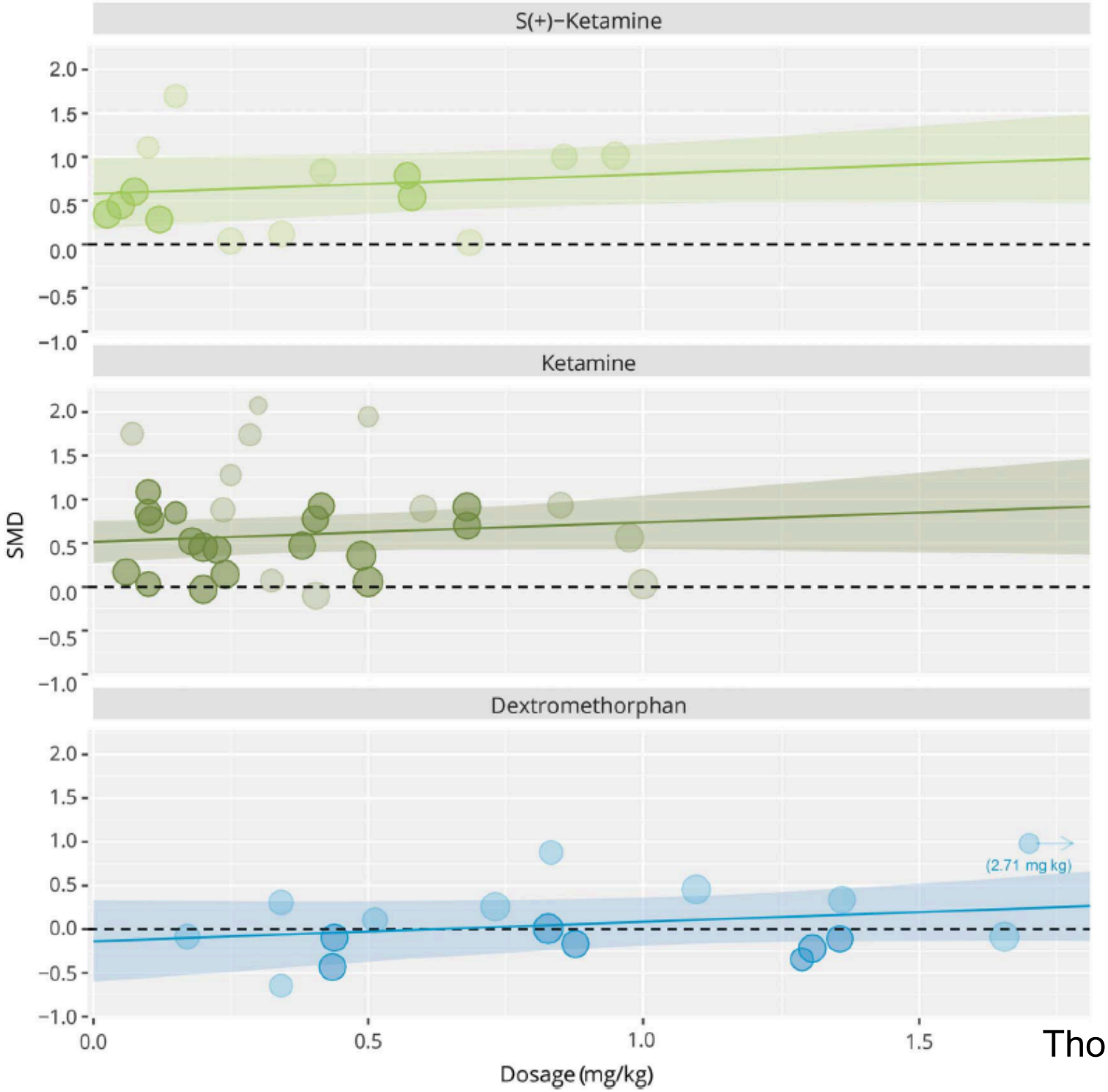
Paljonko?

4 tyypillistä annosaluetta (24 h, 70 kg):
≈10 mg, ≈ 30 mg, ≈ 65 mg ja ≈ 250 mg

”no increased morphine-sparing effect on increasing ketamine dose > 30 mg (24 h/70 kg)” Bell et *al.* 2005

		Effect size (SDM)	95%CI	
≤0.5 mg/kg	32	−0.589	−0.813	−0.366
0.501–1 mg/kg	6	−0.038	−0.252	+0.175
>1 mg/kg	20	−0.808	−1.121	−0.496

Laskowski et *al.* 2011



Thompson et *al* 2019

Ketamiini ivPCA:ssa

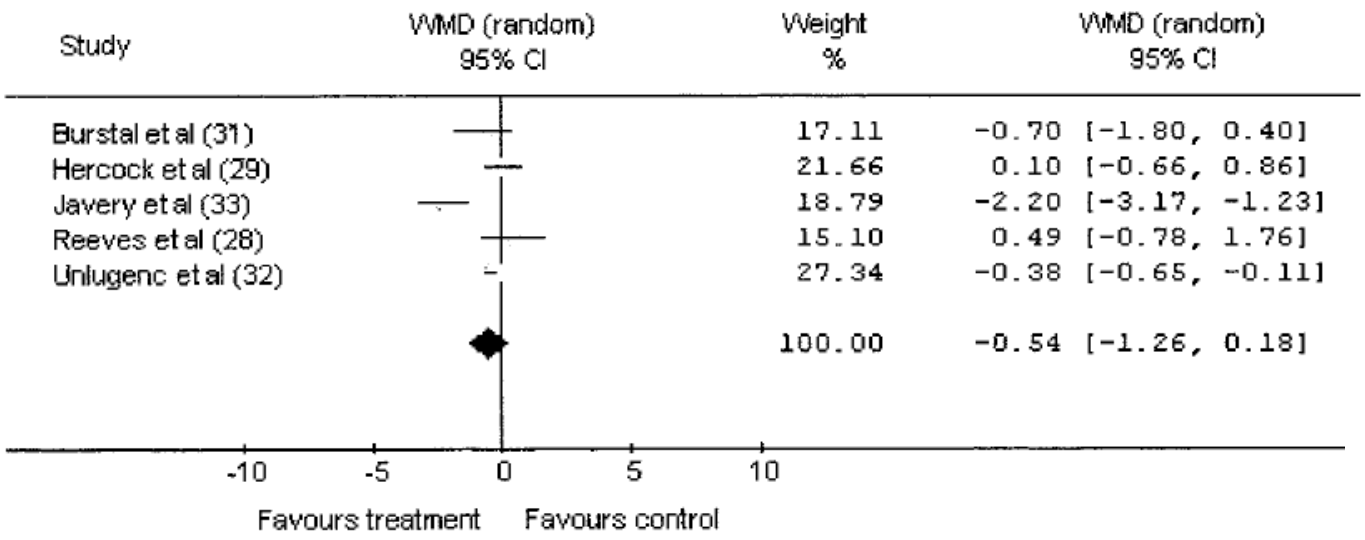


Figure 1. Intravenous patient-controlled analgesia with morphine in patient-controlled analgesia (visual analog scale at rest). WMD = weighted mean difference; CI = confidence interval).

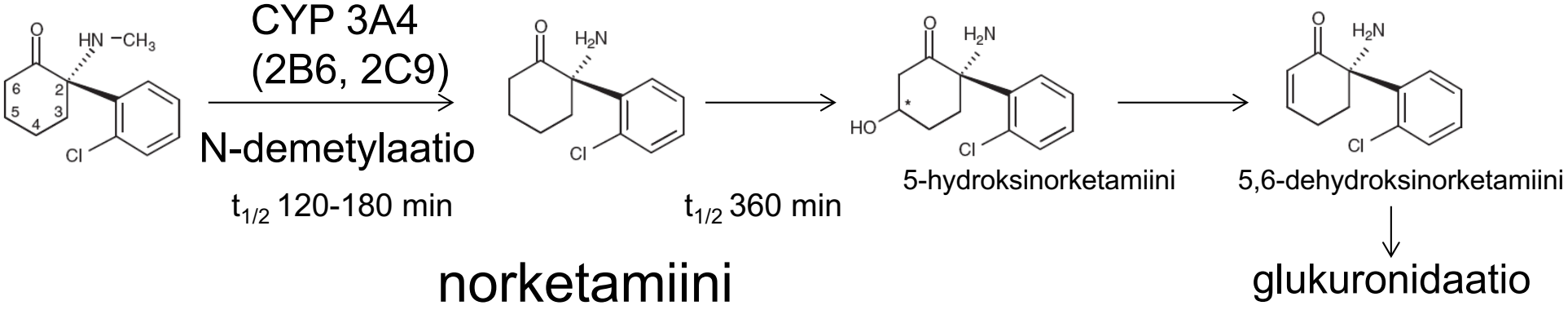
Subramaniam et *al* 2004

- heterogeenisia tutkimuksia +++ – – Elia & Tramèr 2005
- +++ +/- (–) – – Bell et *al* 2005
- ++++++ – – – – – Carstensen & Møller 2010
- thoracic surgery +
- orthopaedic or abdominal surgery - ?

Tutkimusnäyttö syöpäkivun hoidossa

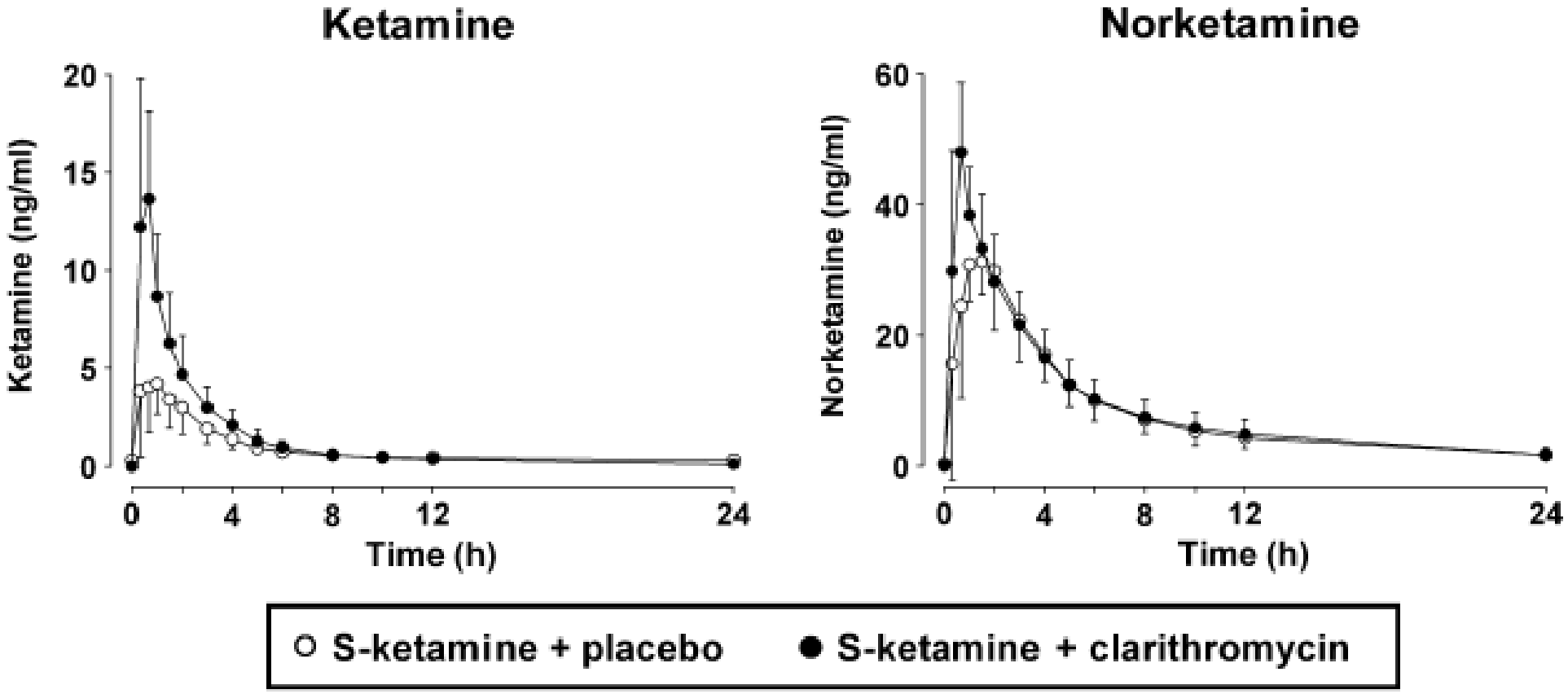
Mercadante et al. 2000 0.25 / 0.5 mg/kg iv	10	Reduced pain intensity in almost all the patients at both doses. Effect more relevant with higher doses. Hallucinations in 4 pts, unpleasant sensation in 2 pts.
Lauretti et al. 1999 0.5 mg/kg x2 po	15	Decreased opioid consumption on days 15-30, somnolence.

Bell et al. 2003
Prommer 2012



norketamiini

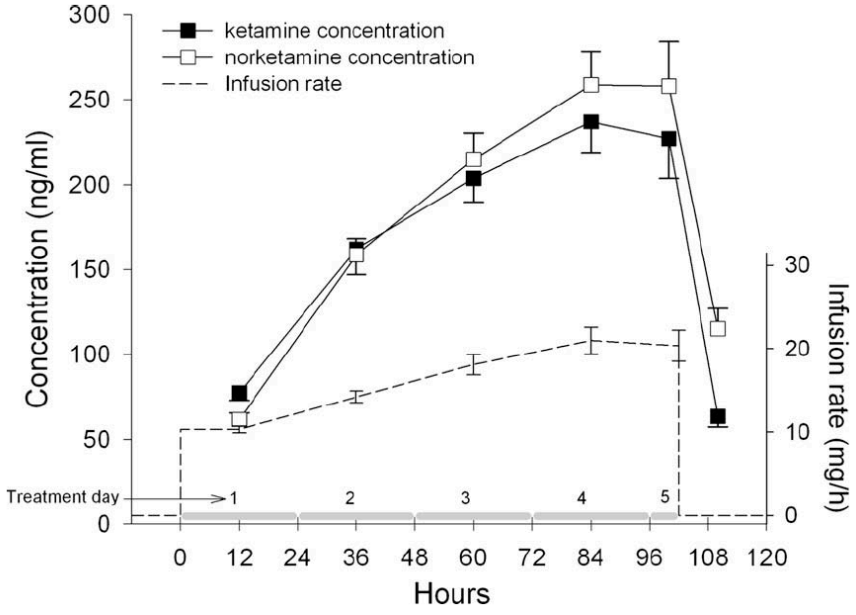
- enantiomeeriselektiivinen metabolia S>R
- oraalinen hyötyosuus (S) 17-24%

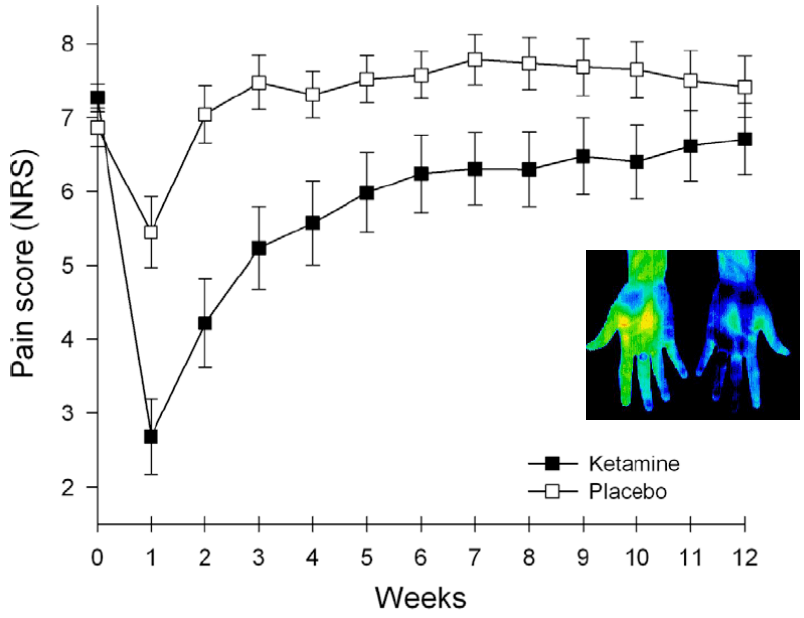


- (pienillä annoksilla) ei vaikutusta kokeelliseen kylmäkipuun ihmisellä

Hagelberg et al. 2009

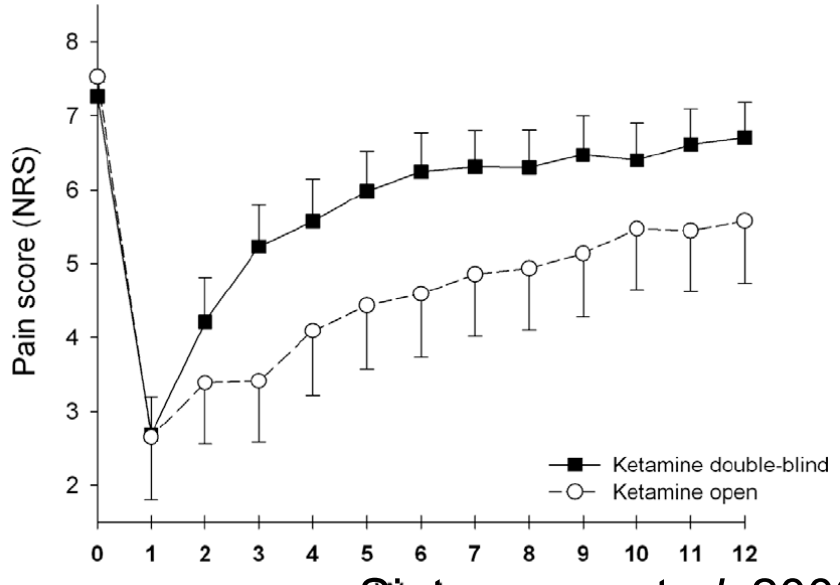
CRPS





- 2 rct + 7 observ + 9 cases
- 0.35 ug/kg/h – 7 mg/kg/h
- 4h(x10) – 240 h

Schwartzman et *al.* 2009
review: Azari et al. 2012,
Schwartzman et *al.* 2011



Sigtermans et *al.* 2009

Haitat

- painajaiset, dysforia, hallusinaatiot, delirium
- (neurotoksisuus?)
- (väärinkäyttöpotentiaali)
- (kystiitti, maksatoksisuus)
- CNS aktivaatio -> hapenkulutuksen ja aivopaineen nousu?

Category	Effects
Emergence phenomena	Vivid dreams and/or imagery, hallucinations, delirium, floating sensations, extra corporeal experiences, 'weird trips', misperception of visual stimuli, auditory misperception, synaesthesia, temporal and spatial disorder, body detachment, dissociative state, sensation of being separated from environment and/or body and enhanced colour vision
Cognitive	Concrete thinking, impaired episodic memory, deficit prepulse inhibition, reduced verbal recall, reduced attentional performance, impaired performance on tests of vigilance, acute amnesic effects, poor recognition memory (verbal), inhibition of long-term potentiation, impaired verbal fluency and perseveration
Psychotic	Emotional withdrawal, lack of interest, disorganised speech, blunted affect, formal thought disorder, paranoid ideation, lack of responsive awareness, ideas of reference, time delusion, mistrust, raised suspiciousness and unusual thought content

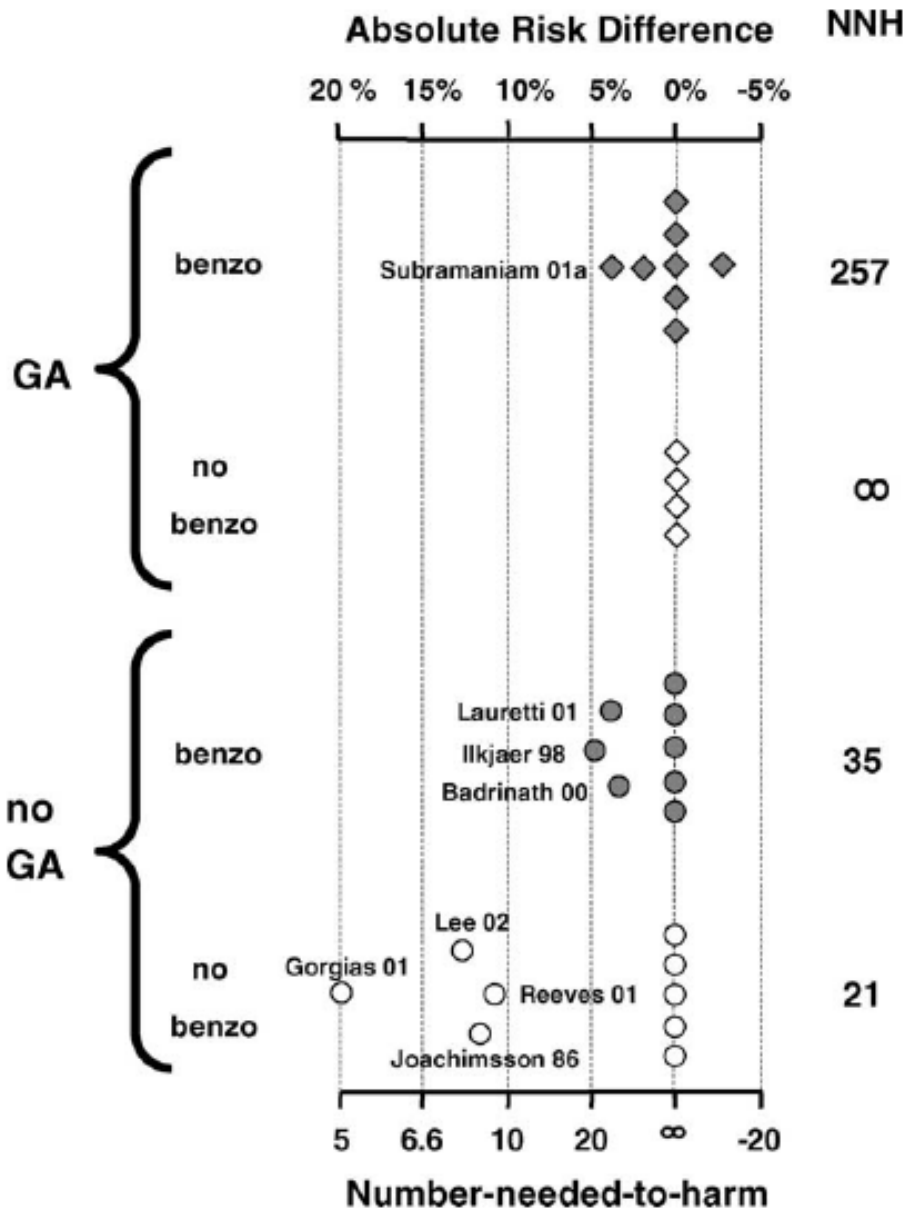
Wolff & Winstock 2006

- hallusinaatiot

- painajaiset
  NNH 62
- miellyttävät unet
  NNT 12
- näköhäiriöt
  NNH 28

- iäkkäillä ja/tai kriittisesti sairailla suurempi riski?

- annos!



Elia & Tramèr 2005

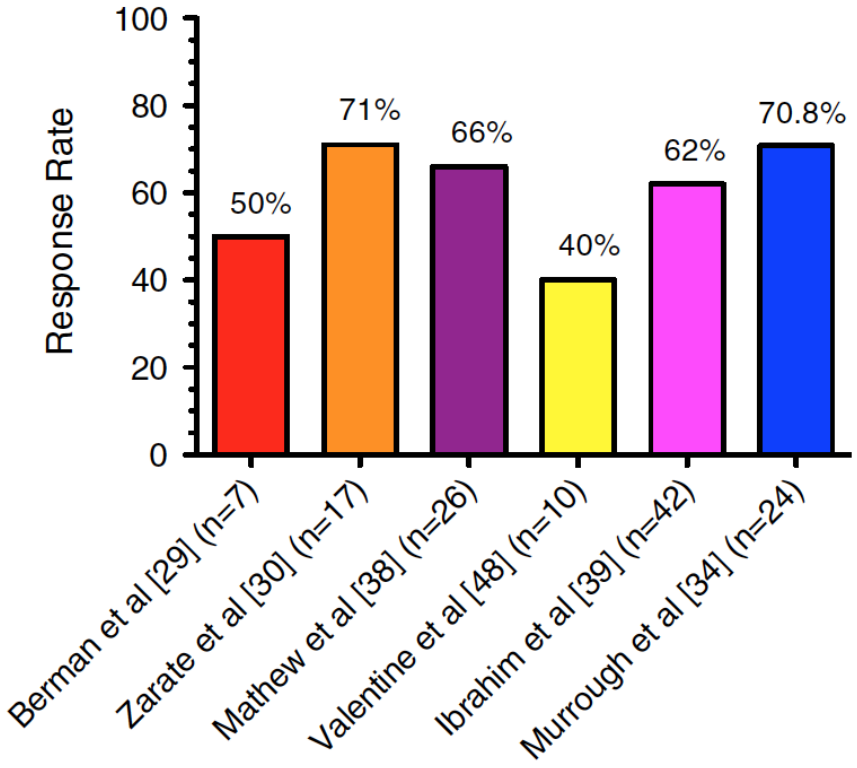
- CNS adverse events in 187 pts (5 %) in ketamine groups vs 122 pts (4%) in control groups (NS).
- Results were no different in studies using benzodiazepine premedication.

Brinck et *al.* 2018

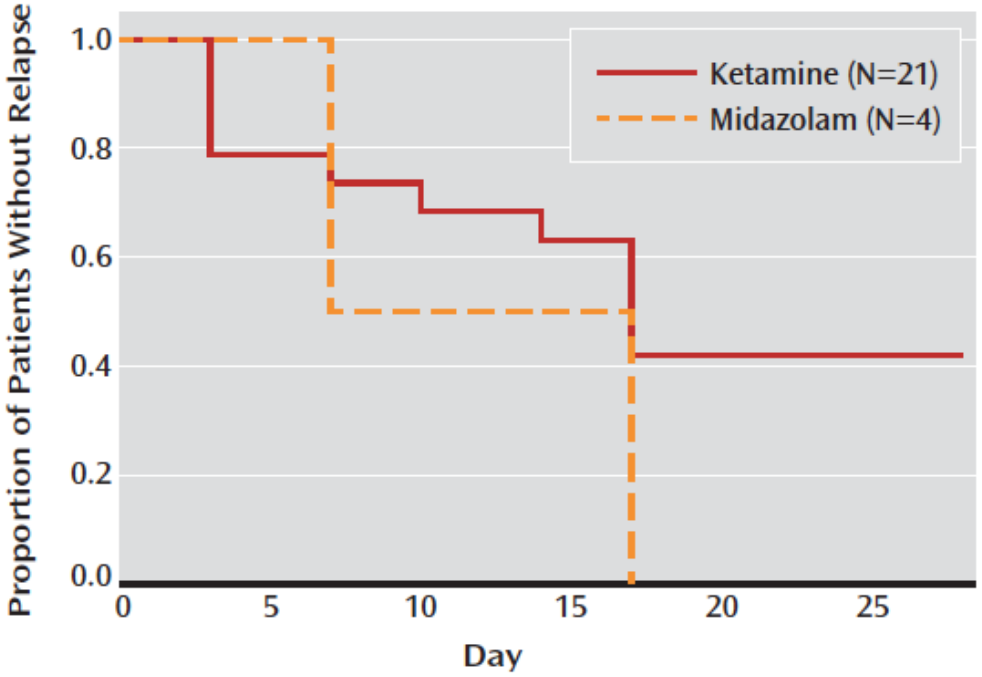
- In a large (672 participants) recent study on postoperative delirium no difference between ketamine (0.5 mg/kg and 1.0 mg/kg bolus doses) and placebo in postoperative delirium (19% for ketamine and placebo)

Avidan 2017

Ketamiini ja depression hoito



Murrough & Charney 2012



Murrough et al. 2013

Ketamiini ja ECT

- Ketamine + other anesthetics drugs superior in improving depressive symptoms over other anesthetic medications at early study time point, but not at post-ECT or end of study time points (17, 1035 pts).
- Ketamine alone was not more efficacious other anesthetic drugs at early study, post-ECT and end of study time points.

Zheng et al 2019

Johtopäätökset

- ketamiini vähentää opioidin tarvetta (25%?) → vähentää opioidin haittavaikutuksia
- parantaa leikkauksen jälkeisen kivun lievitystä
- pienillä annoksilla haittavaikutukset vähäisiä

- ei rutiinikäyttöön
- ≈ 0.02 mg/kg/t iv suuren leikkauksen jälkeen erityisen kipeille potilaille

- suuria opioidiannoksia käyttävät potilaat?

Tulevaisuudessa

- tarvitaanko lisää tutkimuksia ketamiinista akuutin kivun hoidossa?
  - erityisryhmät
  - kivun kroonistuminen
  - annos
  - haittavaikutukset

- potentti ei-HCN1-salpaaja NMDA-antagonisti analgeetiksi ja opioiditoleranssin kumoamiseen / estoon?
- non-NMDA-antagonisti HCN1-salpaaja anesteetiksi??