Sedation in children

SPAN Nov 2011

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Pharmacological preparation?

Declaration of conflict of interest

Nothing to declare

Reasons for premedication

- Allay anxiety and fear in uncooperative child
- Avoidance of forceful restraint
- Facilitate induction of anaesthesia (iv or inhalational)
- Antisialagogue and anticholinergic

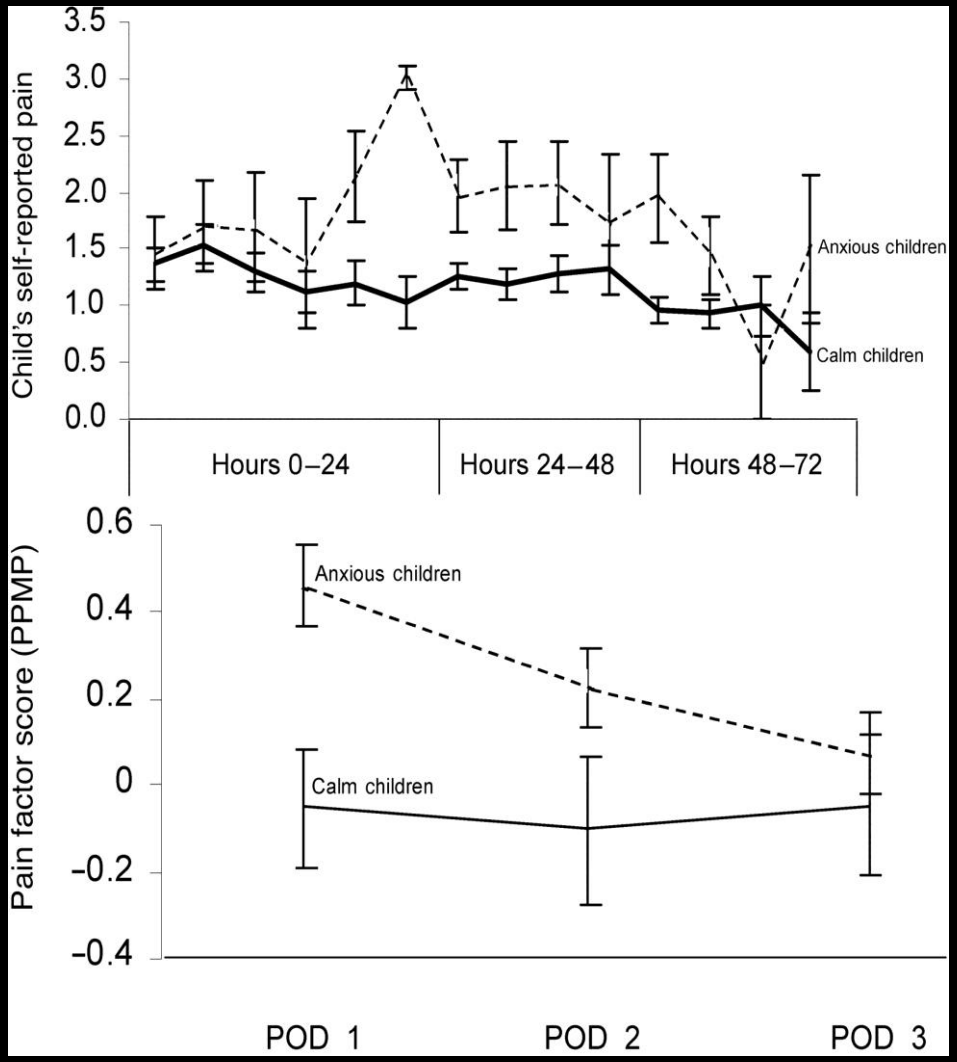
Does it matter?

Reasons for premedication - does it matter?

Kain et al (2006)

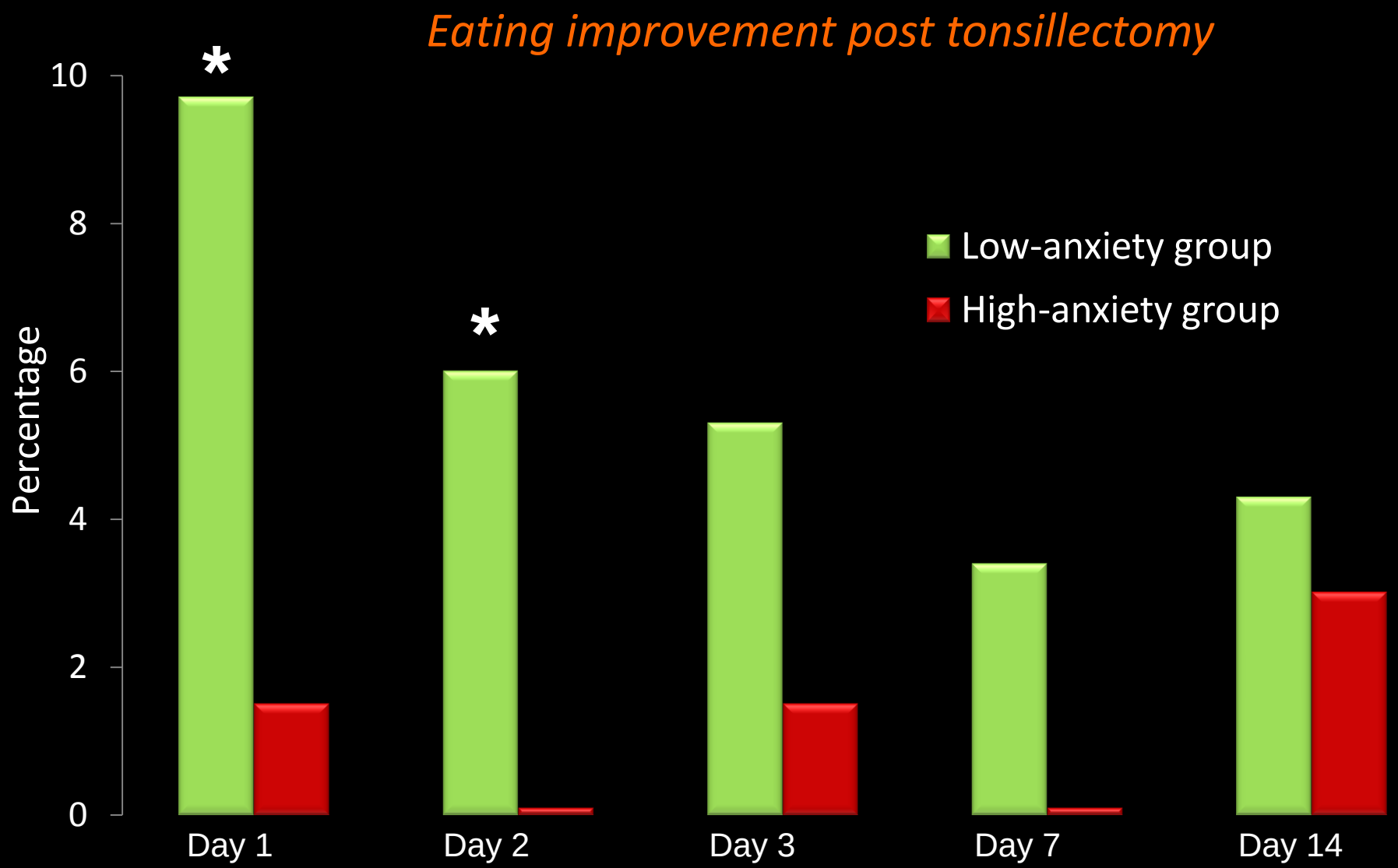
Children: > 6 yo (n=241)
Elective adeno-tonsillectomy
Anxious vs calm children (m-YPAS)

- Higher self reported pain
- Higher parent reported pain
- Higher emergence delirium (9.7% vs 1.5%)
- Higher postoperative sleep problems



Pediatrics 2006;118:651-658

Reasons for premedication - does it matter?



Pediatrics 2006;118:651-658

Ideal premedication drug

- Tasteless
- Odourless
- Colourless
- Stable when mixed
- Reliable and reproducible dose dependent anxiolysis
- Routes of administration (PO, PR, IM, intranasal…)

… Does not exist

What is available?

Commonly used

- Benzodiazepines
- α_2 receptor agonists
- Ketamine
- Opioids

Older preparations

- Chloral hydrate and triclofos

New developments

- Melatonin and analogues
- Oxytocin (?)

Benzodiazepines

Most commonly used

- Midazolam (0.5-0.7 mg/kg)
- Diazepam (0.3-0.5 mg/kg)
- Temazepam (0.5 mg/kg)
- Lorazepam (0.05 mg/kg)

Gamma-aminobutyric acid receptor complex

Anxiolysis, sedation and amnesia

Benzodiazepines - Midazolam

General Remarks

- Most widely used sedative premedication
- Route and parental preparation
- Plasma concentrations correlate with clinical effect
- Bitter taste, nasal administration very irritant
- Higher doses - delayed emergence and recovery
- Paradoxical excitation

Benzodiazepines - Midazolam

Pharmacokinetics

- Potentially highly variable
- Active metabolite (1OH midazolam)
- Bioavailability and time to peak plasma concentration
  - Oral: 0.27-0.36 and 30-60 min
  - Nasal: 0.55 and 10-15 min
  - Rectal: approx 10 min
- Clearance
- Elimination $t_{1/2}$

Benzodiazepines - Midazolam

Clinical data

Safety: Effects on respiratory function

Children: 3-8 yo (n=18)
Midazolam 0.3 mg/kg 20 min

Table 1. Changes in Respiratory Variables Before and After Premedication with Midazolam

	Pre	Post	% change	*P*
Functional residual capacity (mL/kg)	25.0 (1.4)	23.4 (1.9)	−6.5 (5.0)	<0.001
Lung clearance index	6.40 (0.4)	6.89 (0.4)	7.8 (7.0)	<0.001
Tidal volume (mL/kg)	8.64 (1.4)	8.40 (1.5)	−3.0 (4.9)	0.025
Respiratory rate (per min)	24.6 (3.0)	24.1 (2.9)	−1.7 (5.5)	0.176
Minute ventilation (mL/kg)	213 (47)	202 (46)	−4.7 (6.9)	0.006
Raw (cm H_2O s/L)	3.38 (0.6)	3.62 (0.6)	7.4 (8.8)	<0.001
H (cm H_2O/L)	48.8 (9.7)	52.9 (9.1)	9.2 (8.5)	<0.001

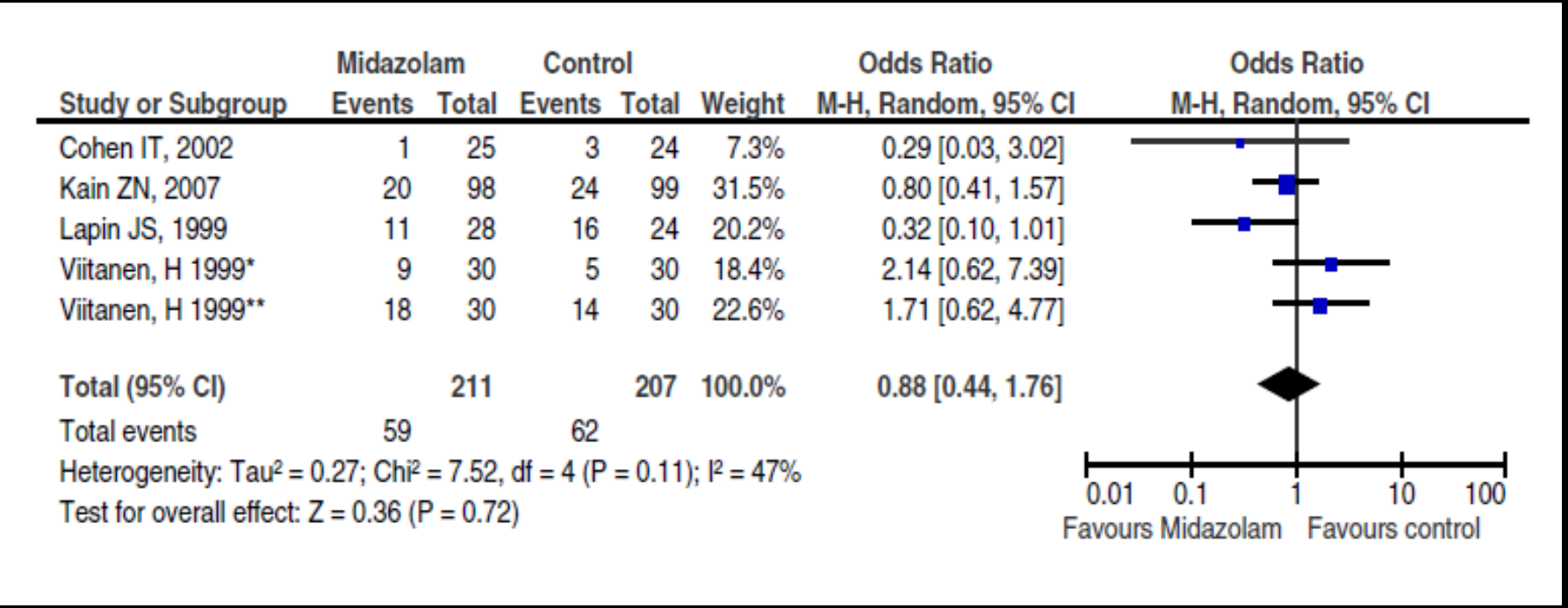
Values are given as mean (SD). Significances as determined with a paired *t*-test.

Anesth Analg 2009; 108: 1771

Benzodiazepines - Midazolam

Clinical data

Midazolam does not prevent sevoflurane ED



Study or Subgroup	Midazolam Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Cohen IT, 2002	1	25	3	24	7.3%	0.29 [0.03, 3.02]
Kain ZN, 2007	20	98	24	99	31.5%	0.80 [0.41, 1.57]
Lapin JS, 1999	11	28	16	24	20.2%	0.32 [0.10, 1.01]
Viitanen, H 1999*	9	30	5	30	18.4%	2.14 [0.62, 7.39]
Viitanen, H 1999**	18	30	14	30	22.6%	1.71 [0.62, 4.77]
Total (95% CI)		**211**		**207**	**100.0%**	**0.88 [0.44, 1.76]**
Total events	59		62			

Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 7.52$, df = 4 (P = 0.11); $I^2 = 47\%$

Test for overall effect: Z = 0.36 (P = 0.72)

BJA 2010; 104:216

Benzodiazepines - other

- Diazepam
  - Water insoluble
  - Prolonged elimination $t_{1/2}$
  - Peak 60-90 min
- Temazepam
  - Tablet and elixir form
  - Peak 90 min
- Lorazepam
  - Prolonged amnesia
  - Peak 90 min

α_2 receptor agonists

General Remarks

- Inhibit release of NA and sympathetic activity
- Effects via $G\alpha_i$ ($AC\downarrow$, K^+/Ca^{2++})
- Binding to receptors in LC and spinal cord

Clinical Effects

- Decrease HR, BP
- Sedation , anxiolysis
- Analgesia

α_2 receptor agonists - clonidine

Pharmacokinetics

- Little known in children
- Erratic absorption
- Peak plasma concentration 30-180 min
- Hepatic biotransformation (p-OH clonidine)
- Renal excretion 50%

α_2 receptor agonists - clonidine

Premedication

- 4 mcg/kg taste, colour & odourless (autistic)
- 'Steal' induction
- No effect on
  - Cognitive function or memory
  - Respiratory drive
- Positive effects
  - Reduced anaesthetic requirements & analgesia
  - Less postoperative confusion/ agitation/ ED

α_2 receptor agonists - dexmedetomidine

Pharmacokinetics

- Very limited data
- Bioavailability (16% oral and 82% buccal)
- 8 times more selective than clonidine

Premedication

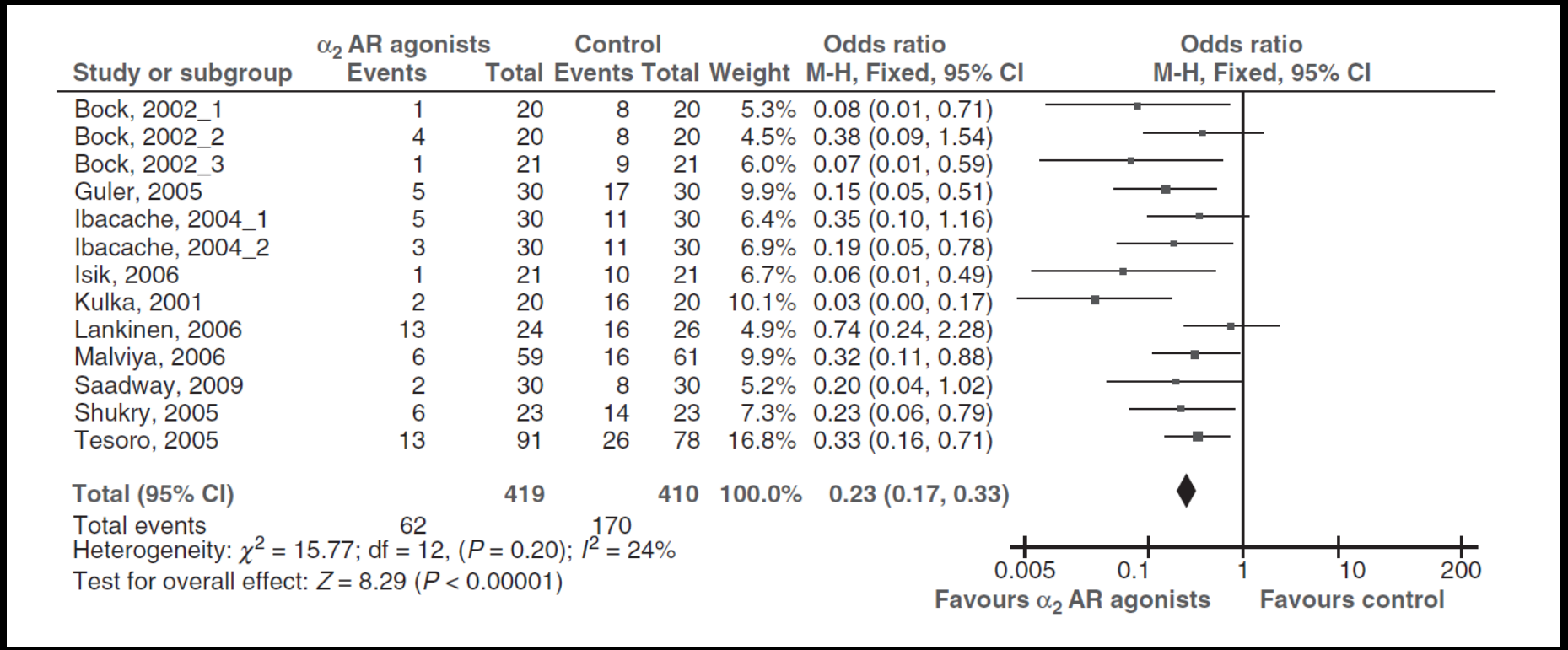
- 2-4 mcg/kg PO or 1mcg/kg buccal
- Taste, colour & odourless (autistic)
- 30-60 min onset time

Paediatr Anaesth 2005; 15:932

α_2 receptor agonists - Benefits

Clinical data

Clonidine and dexmedetomidine prevent sevoflurane ED



Study or subgroup	α_2 AR agonists Events	Total	Control Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI
Bock, 2002_1	1	20	8	20	5.3%	0.08 (0.01, 0.71)
Bock, 2002_2	4	20	8	20	4.5%	0.38 (0.09, 1.54)
Bock, 2002_3	1	21	9	21	6.0%	0.07 (0.01, 0.59)
Guler, 2005	5	30	17	30	9.9%	0.15 (0.05, 0.51)
Ibacache, 2004_1	5	30	11	30	6.4%	0.35 (0.10, 1.16)
Ibacache, 2004_2	3	30	11	30	6.9%	0.19 (0.05, 0.78)
Isik, 2006	1	21	10	21	6.7%	0.06 (0.01, 0.49)
Kulka, 2001	2	20	16	20	10.1%	0.03 (0.00, 0.17)
Lankinen, 2006	13	24	16	26	4.9%	0.74 (0.24, 2.28)
Malviya, 2006	6	59	16	61	9.9%	0.32 (0.11, 0.88)
Saadway, 2009	2	30	8	30	5.2%	0.20 (0.04, 1.02)
Shukry, 2005	6	23	14	23	7.3%	0.23 (0.06, 0.79)
Tesoro, 2005	13	91	26	78	16.8%	0.33 (0.16, 0.71)
Total (95% CI)		**419**		**410**	**100.0%**	**0.23 (0.17, 0.33)**
Total events	62		170			

Heterogeneity: $\chi^2 = 15.77$; df = 12, ($P = 0.20$); $I^2 = 24\%$

Test for overall effect: $Z = 8.29$ ($P < 0.00001$)

BJA 2010; 104:216

α_2 receptor agonists

Clinical data

Clonidine and dexmedetomidine prevent PONV ???

Acta Anaesthesiol Scand 2010; **54**: 397–402
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2009.02207.x

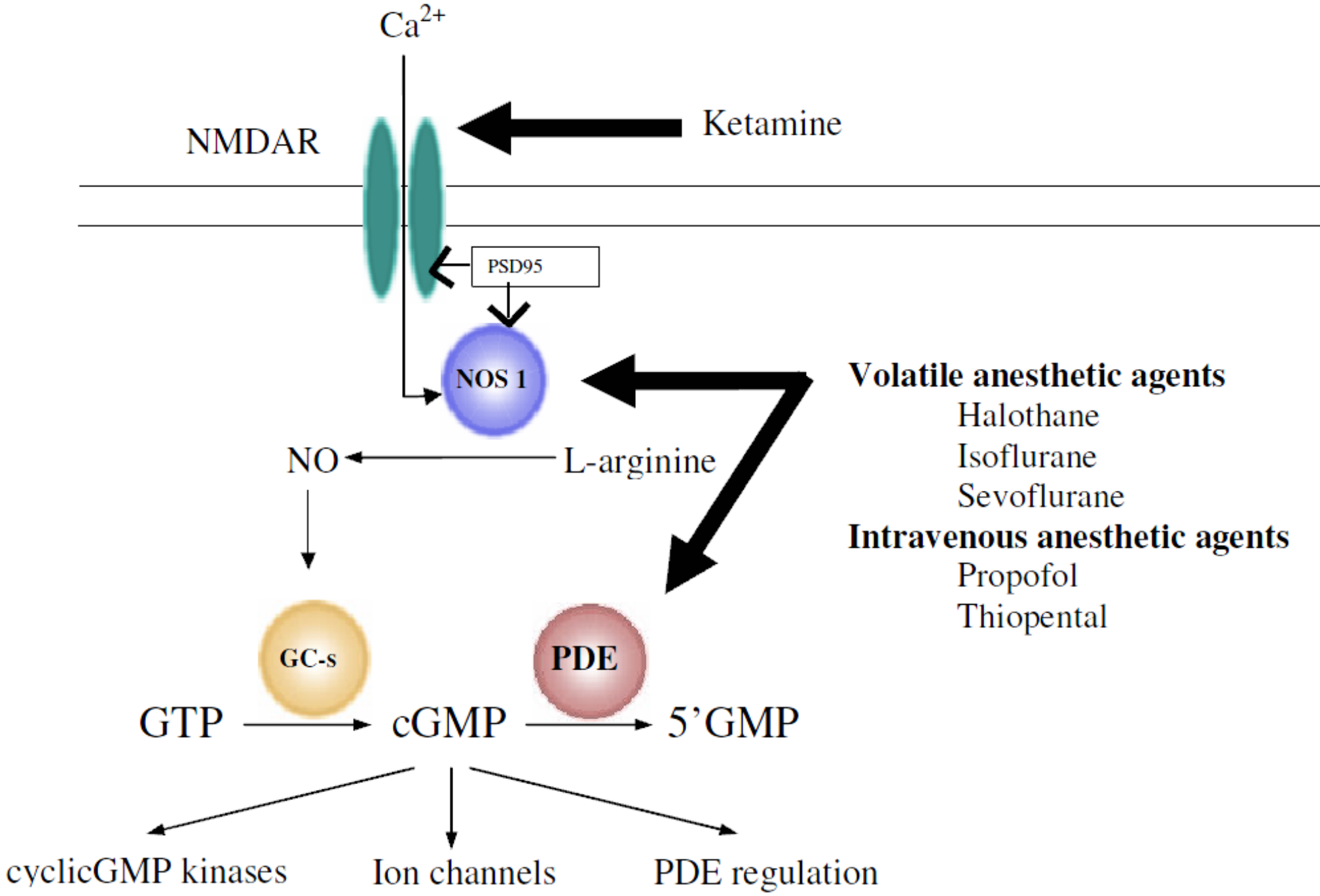
Review Article

Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies

S. DAHMANI[1], C. BRASHER[1], I. STANY[1], J. GOLMARD[1], A. SKHIRI[1], B. BRUNEAU[1], Y. NIVOCHE[1], I. CONSTANT[2] and I. MURAT[2]
[1]*Department of Anesthesiology, Robert Debre University Hospital, Paris, France and* [2]*Department of Anesthesiology, Armand Trousseau University Hospital, Paris, France*

BUT...

The problem with clonidine...



Anaesth Analg 2007; 105:616

Ketamine

Pharmacokinetics

- The higher the dose the faster the onset
- Large V_D, high clearance
- Bioavailability (16% oral to 93% im)

Premedication

- Available in lollipops, elixir and lozenges
- Parental preparation tastes foul
- Onset time <3 min (im) to 30-60 min (PO)

Ketamine

Combination therapy

- Fashionable
- Mixed with benzodiazepines & opioids
- Probably synergistic, no prolonged recovery

Neuronal apoptosis

- Important in animal anaesthesia
- No human clinical equivalent of animal models described

Chloral Hydrate & Triclofos

General remarks

- Bitter taste and gastric irritant
- Standard and established; protocols required
- Serious side effects reported in inadequately monitored patients

Chloral Hydrate & Triclofos

Side effects and profiling

- Prolonged sedation or re-sedation (sick and ex-premature neonates)
- Most effective in children <1 year old; poor >4 years of age
- Good for painless procedures (MRI, CT, echocardiography)

- Doses ranging from 50-100 mg/kg (PO max 2g)
- Onset time is variable:
  - faster with higher dose
  - top-up doses can be given after 20 minutes
- Offset time is variable

- Monitoring: SpO_2, non-invasive BP
- Avoid: Children with obstructive sleep apnoea

Chalkiadis GA ; 2011

Opioids

General remarks

- Occasionally used
- Sedation less pronounced
- Oral preparations available
- Fentanyl 10-20 mcg/kg (PO); 30-45 min optimum
- PONV, pruritus mild

→ Better alternatives

Barbiturates

General remarks

- Available PR, im, iv routes
- Lipid solubility determines onset and $t_{1/2}$
- Methohexital, tiopental, pentobarbital
- Close monitoring
- Irrelevant in modern practice

Melatonin

General Remarks

- Secreted by pineal gland
- Regulating diurnal sleep rhythm
- Frequently used in autistic patients/ jet lag
- Taste, colour and odourless, easily mixed
- Dose range 0.1-0.5 mg/kg peak effect approx 60 min
- ? Effectiveness

Melatonin – Jet Lag

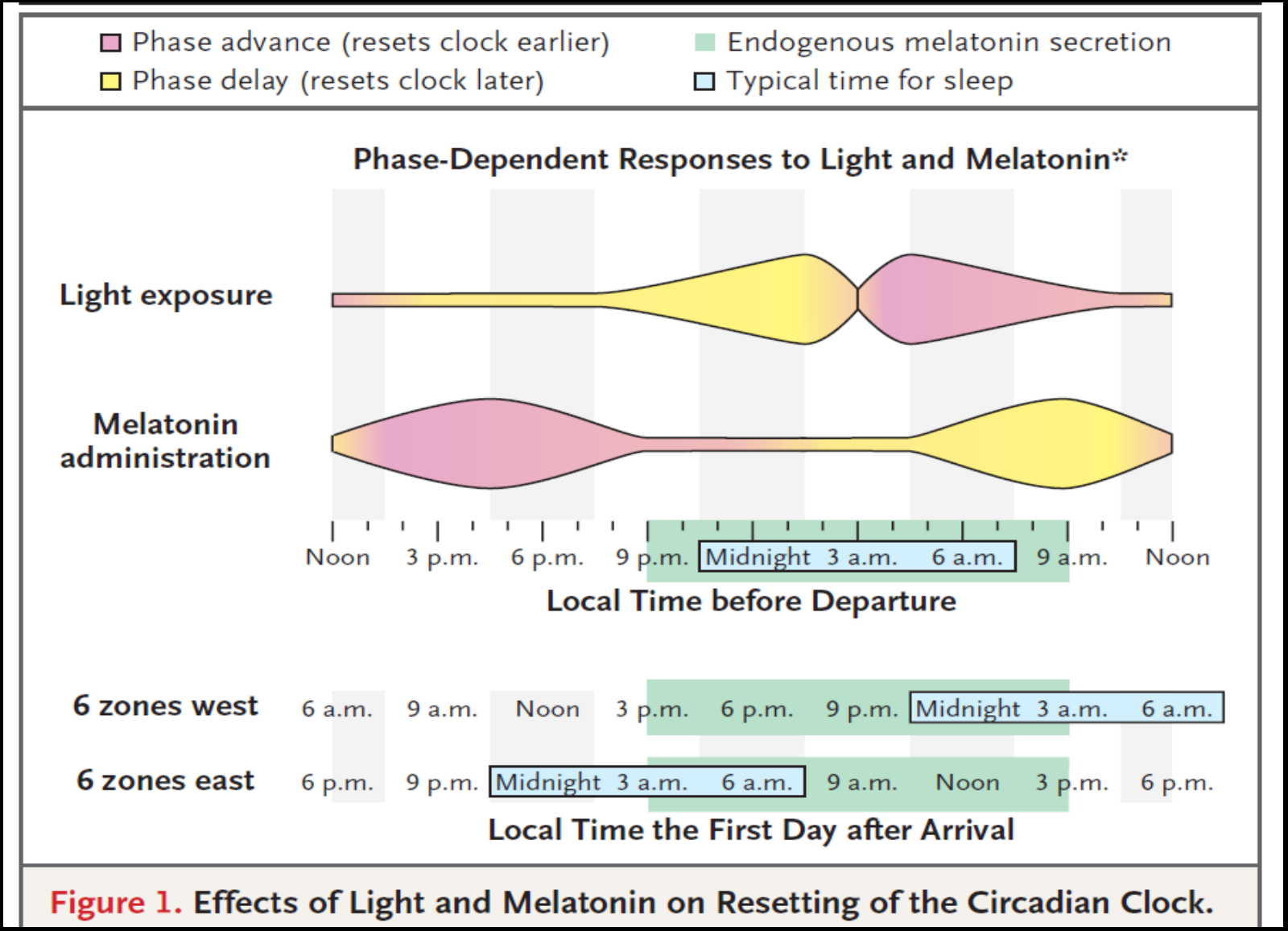


Figure 1. Effects of Light and Melatonin on Resetting of the Circadian Clock.

NEJM 2010; 362: 440

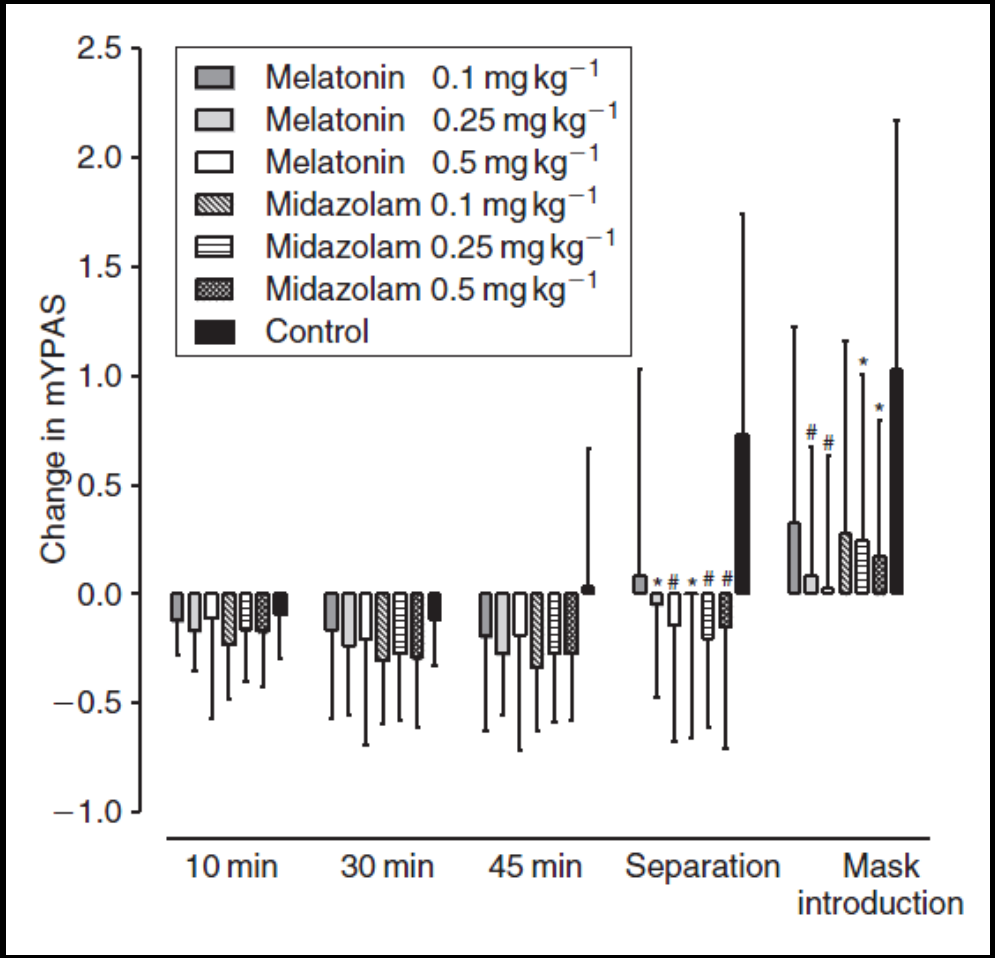
Melatonin

Clinical studies

Limited evidence available

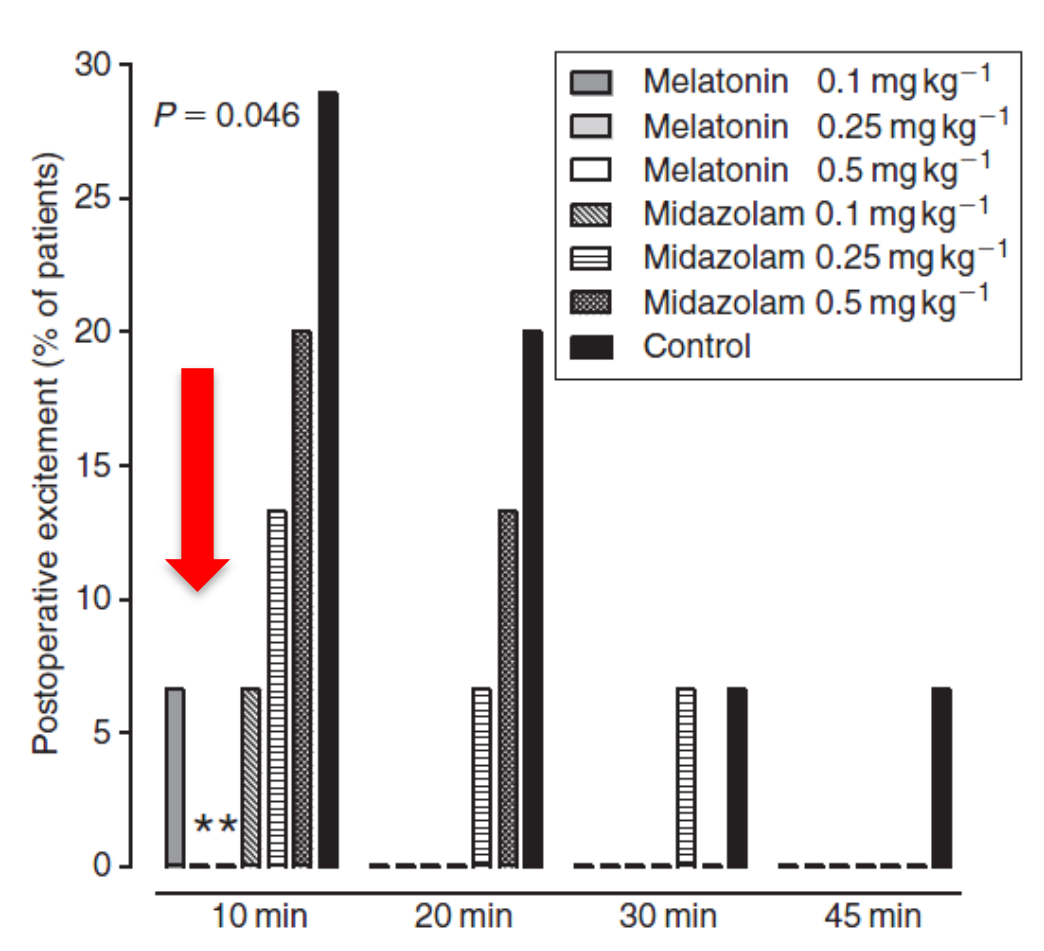
Samarkanid (2005)

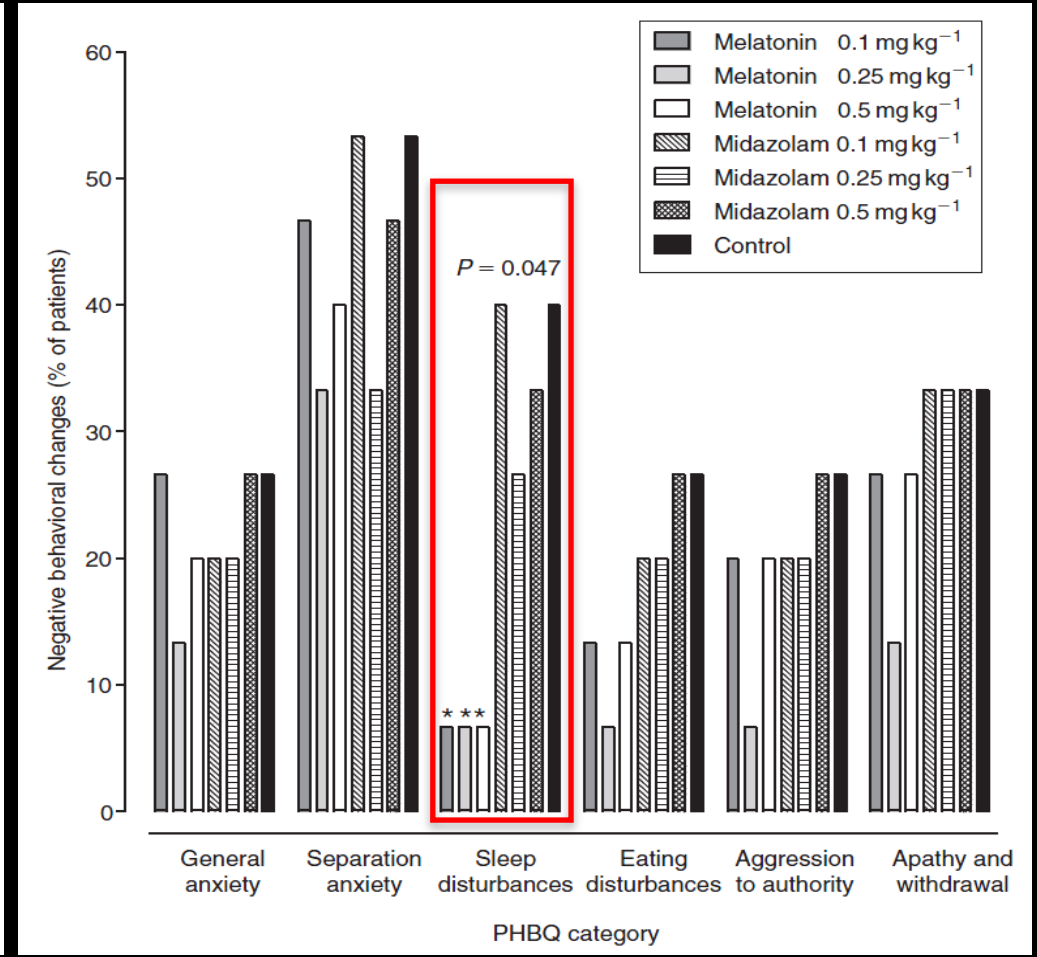
Children: 2-5 yo (n=105), 15 per group
Minor general surgery
3 doses melatonin/ midazolam/ placebo



EJA 2005; 22: 189

Melatonin

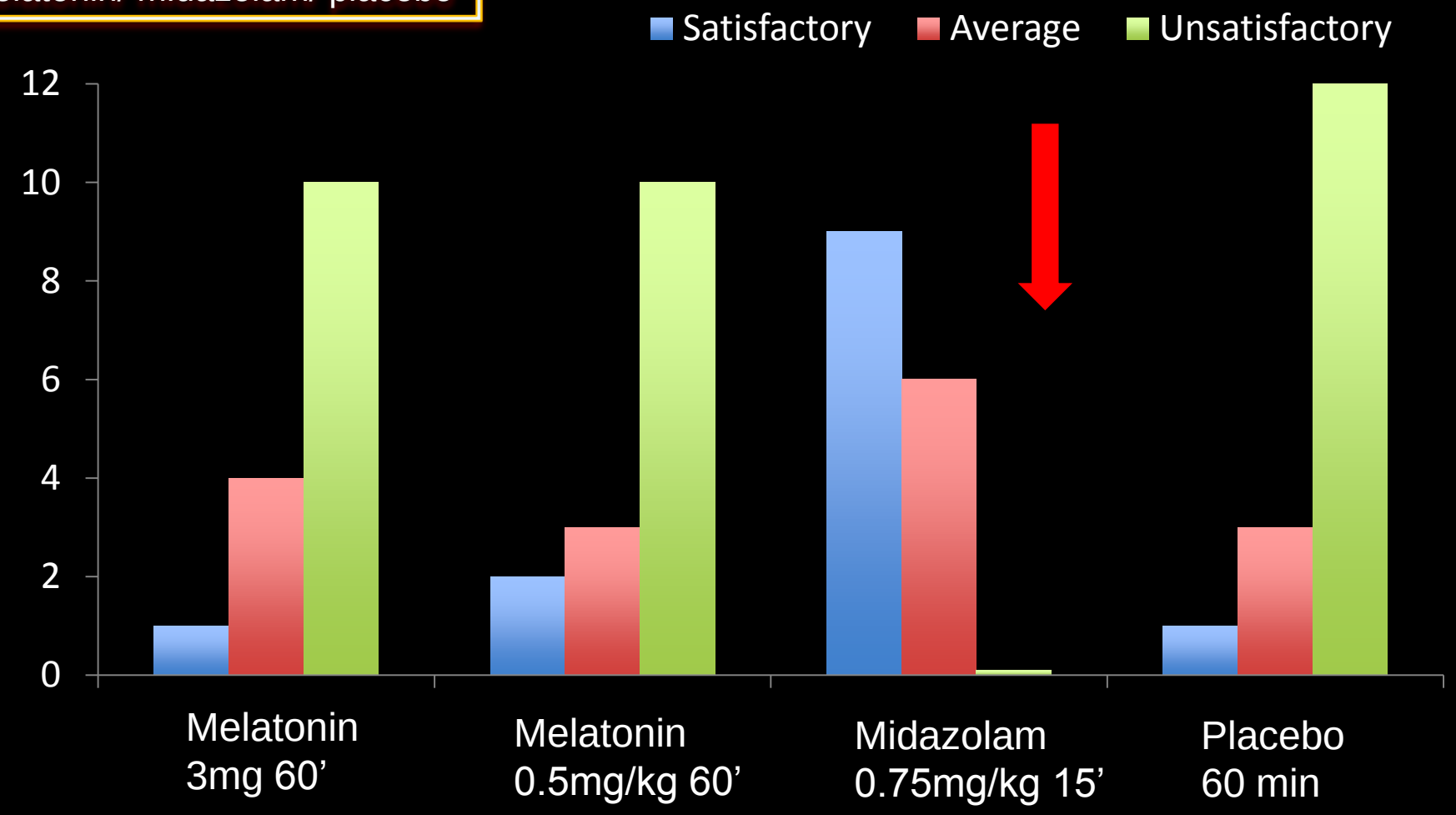




EJA 2005; 22: 189

Melatonin

Children: 4-8 yo (n=60), 15 per group
Sedation dental treatment
2 doses melatonin/ midazolam/ placebo



Paed Anaesth 2008; 18: 635

Melatonin

Side effects	Melatonin (3 mg)	Melatonin (0.5 mg)	Midazolam (0.75mg)	Placebo
Nausea/ vomiting	4	5	5	4
Cough	3	4	2	2
Hiccup	2	1	3	2
Amnesia	-	-	6	

Children: 4-8 yo (n=60), 15 per group
Sedation dental treatment
2 doses melatonin/ midazolam/ placebo

…melatonin patients asleep shortly after treatment

Paed Anaesth 2008; 18: 635

Melatonin

Other studies

- No additional benefit if added to oral sedation regimen
  - Chloral hydrate or temazepam/ droperidol
  - Average dose 0.3mg/kg *(Sury M. BJA 2006; 97: 220)*
- Useful for EEG/ MRI ? *(Wassmer E. Dev Med Child Neurol 2001;43:735)*
- Route relevant (PO vs SL) ? *(Naguib M Anesth Analg 2000; 91: 473–479)*

- Limited pharmacokinetics data in children
- M1 and M2 receptor agonists (Tasimelteon, Remelteon)

Oxytocin

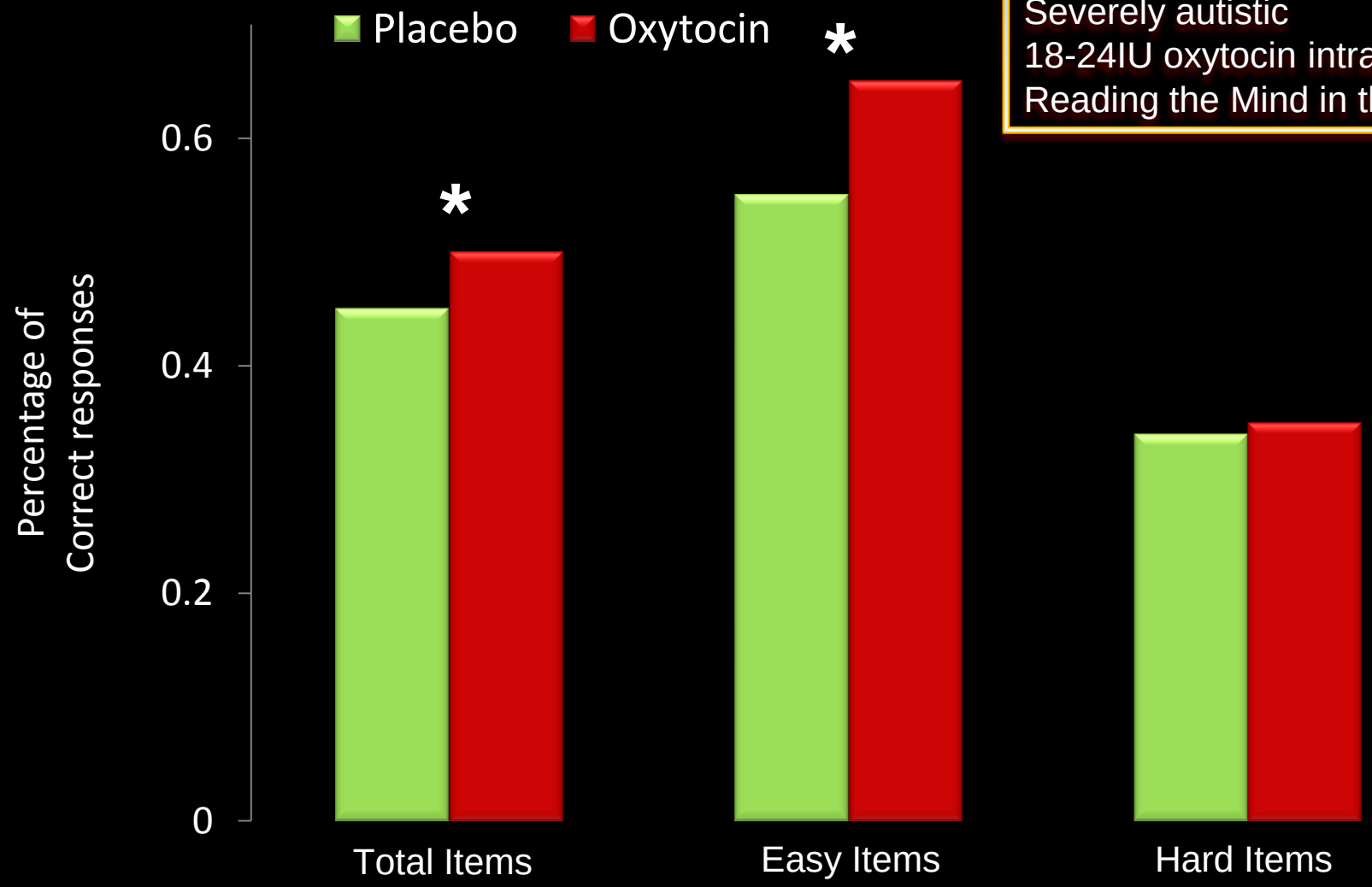
General remarks

- Nonapeptide secreted from posterior pituitary gland
- Key role in social behaviour
  - Peer recognition
  - Social approach and bonding
  - Emotion recognition
- IV or mucosal application

Oxytocin

Improves emotion recognition for youths with autism spectrum disorders

Juveniles: 12-19 years (n=16)
Severely autistic
18-24IU oxytocin intranasally cross over
Reading the Mind in the Eyes Test (RMET)



Biol Psychiatry 2010; 67: 692

Oxytocin

Improves emotion recognition for youths with autism spectrum disorders

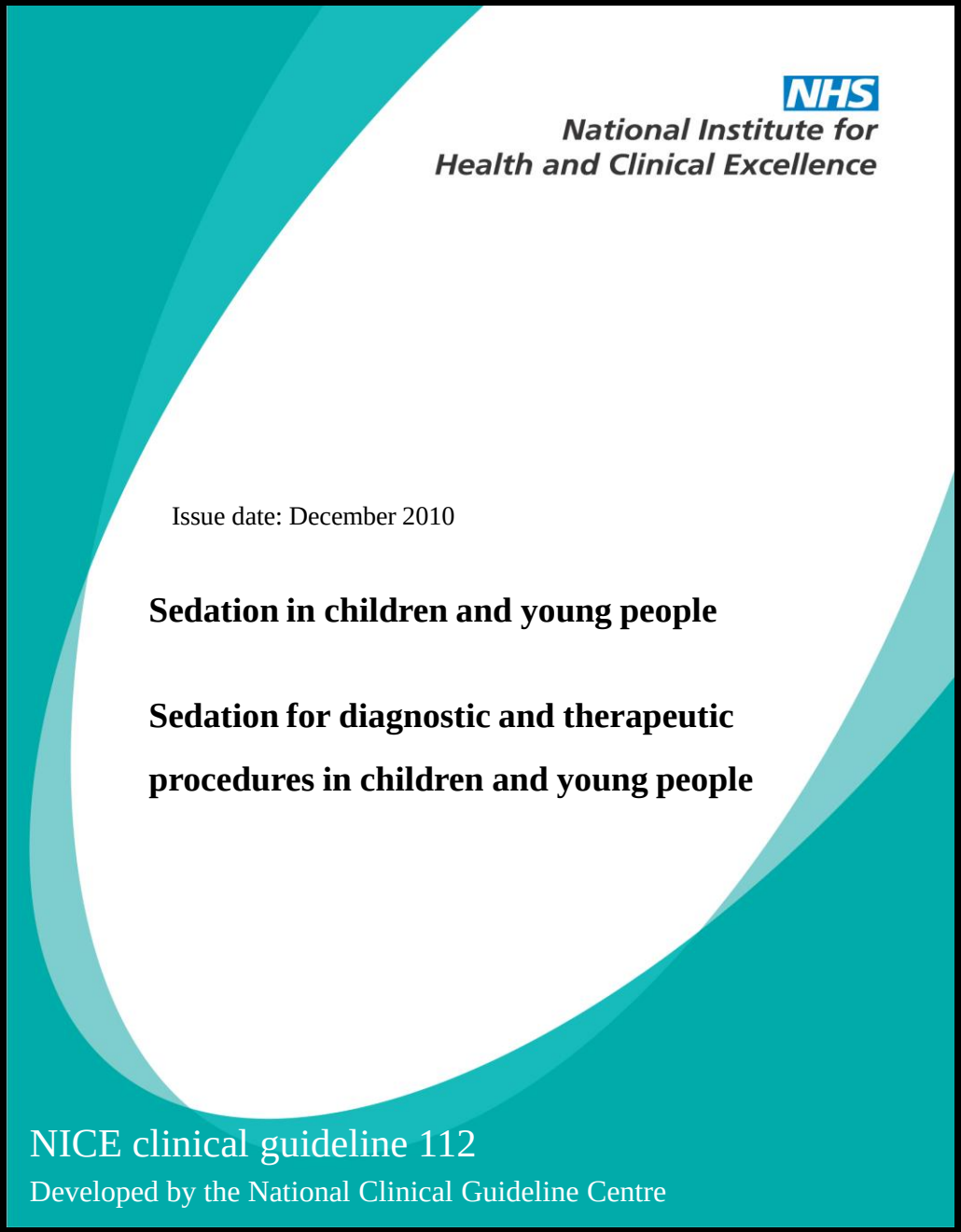
Face mask preparation ?

Data unlikely from UK centres

Summary

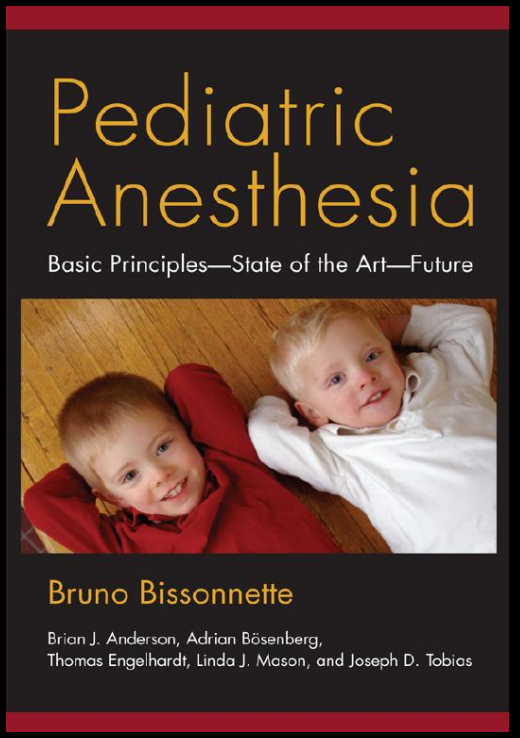
- Anxious patients have worse (surgical) outcomes
- Little published evidence that sedative premedication makes substantial difference
- Single ‘ideal premedication’ agent does not exist
- Selective sedative premedication and combination existing agents adapted to local practice

Further guidelines



Thanks !

Further Reading:
Children of the World Anaesthesia Foundation



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How to avoid sedation….

- Ingenuity
  - What works:
    - Distraction
    - Re-interpretation
  - What does not work:
    - Threatening
    - Reassurance
    - Bribery