

Postoperative treatment



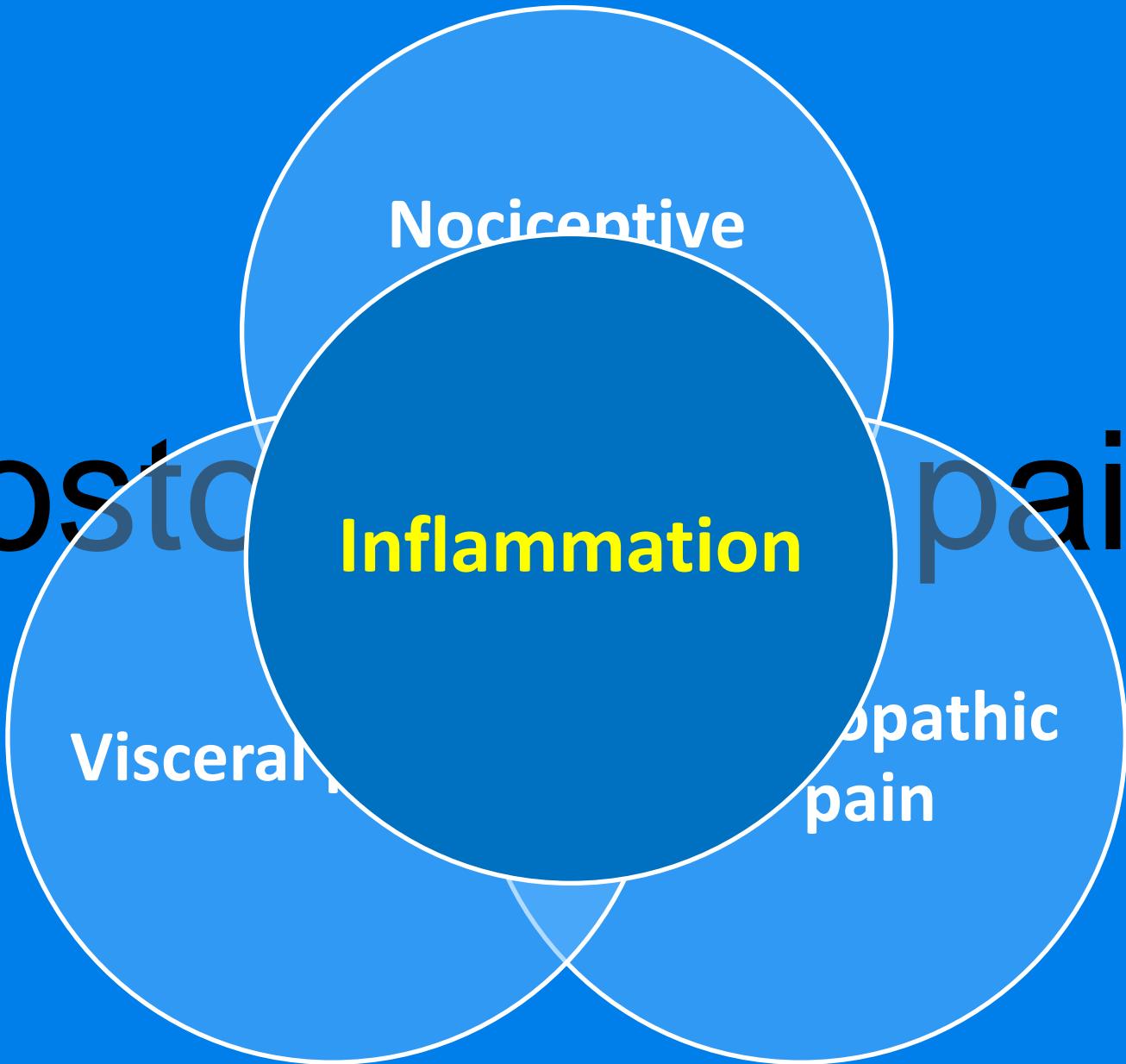
What's the evidence,
- and how to use it?

Ole Mathiesen, MD, PhD
Section for Acute Pain Management
Rigshospitalet, Denmark

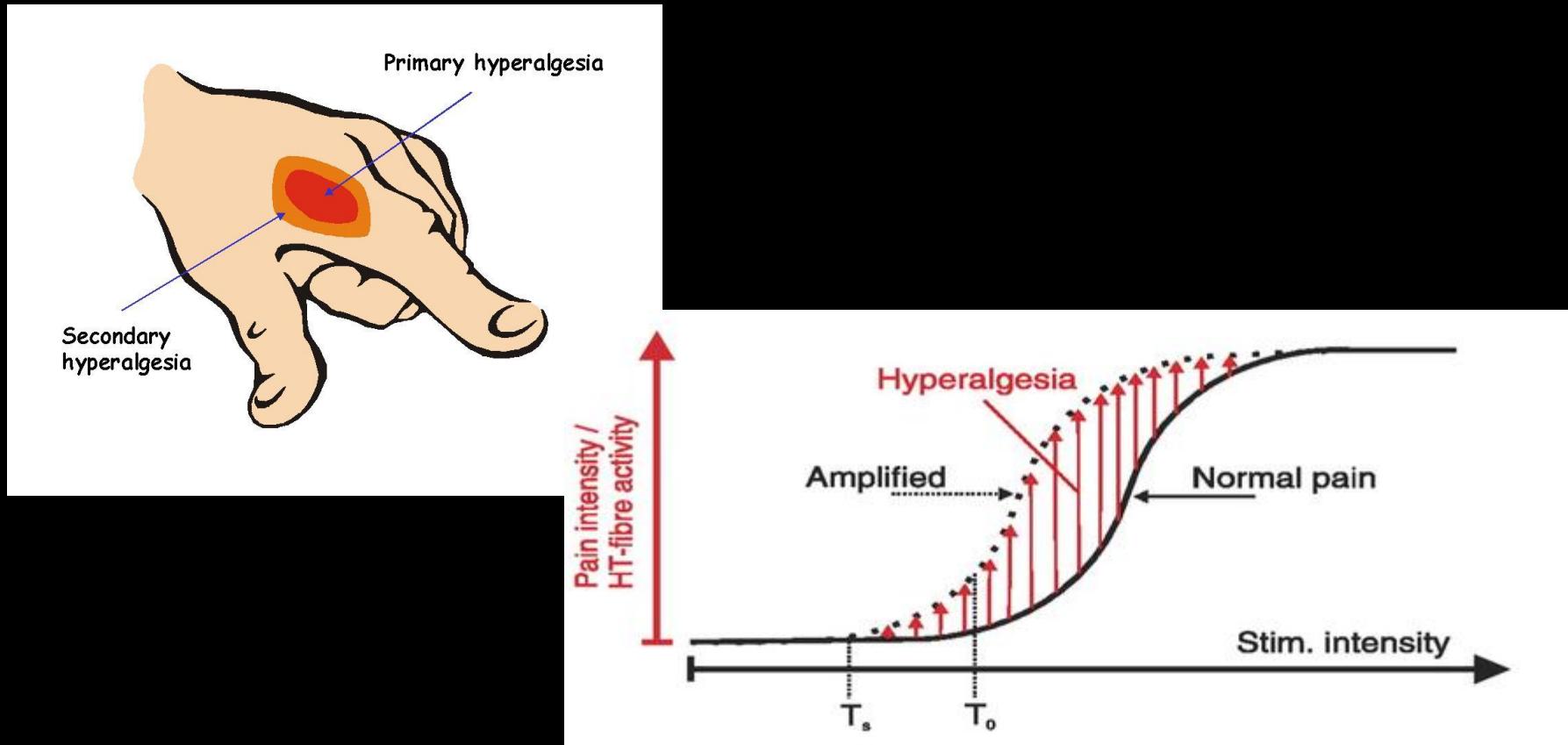
The challenge

- Effective postop pain (POP) treatment: a pre-requisite for convalescence
- International surveys* :
 - 75%: has postoperative pain
 - 30%: moderate to severe pain
- “lack of real breakthrough’ in pain treatment - no new drugs in 50 yr’s” Kissin (A&A 2010)

Post
pain



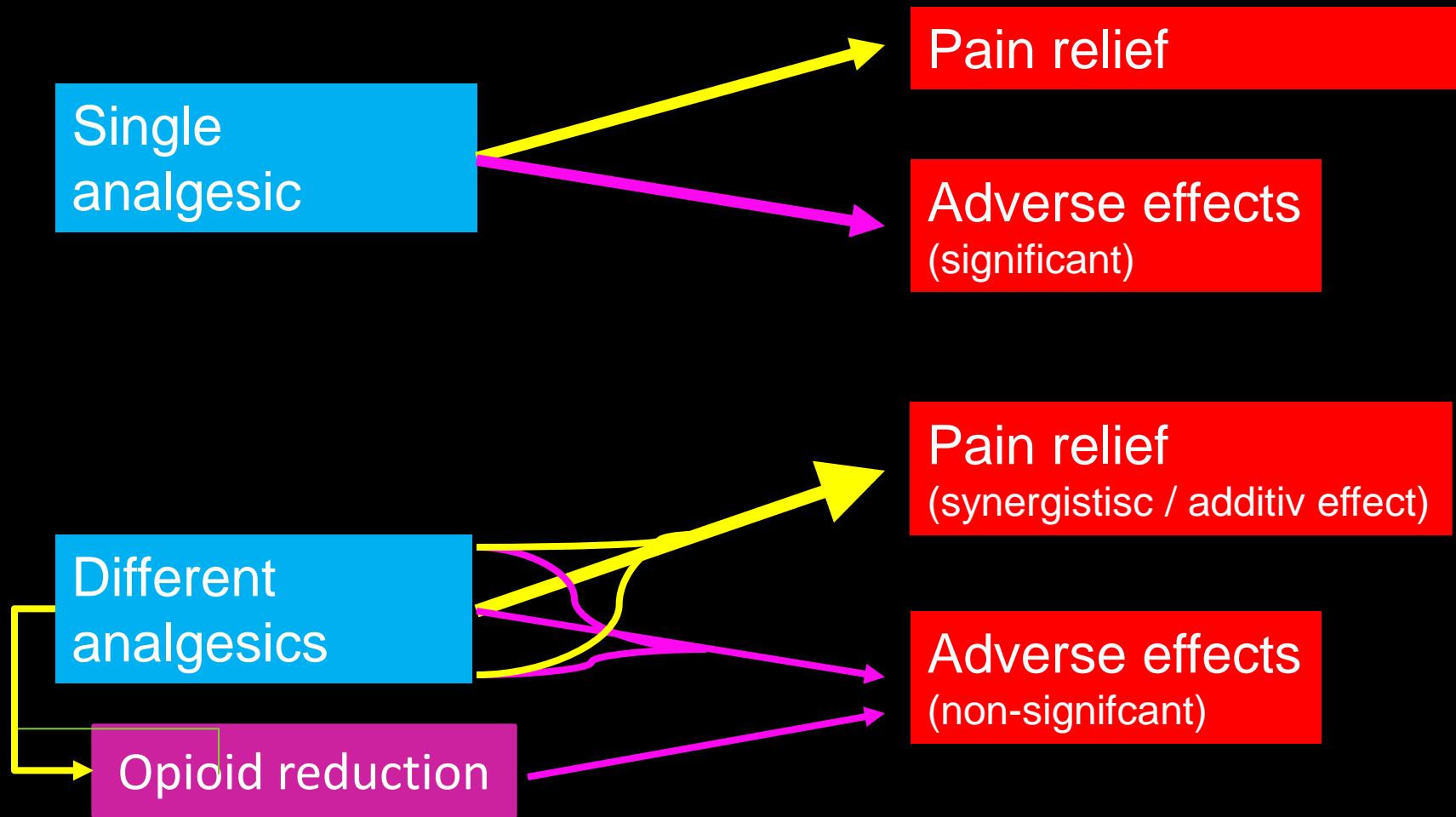
Consequences from peripheral inflammation and central sensitization → increased POP



The Value of “Multimodal” or “Balanced Analgesia” in Postoperative Pain Treatment

Henrik Kehlet, MD, PhD, and Jørgen B. Dahl, MD

Anesth. Analg. 1993



Paracetamol / Acetaminophen

Remy (BJA 2005)

Opioid reduction:
20% / 24h

Toms Cochrane 2008

- 51 RCT & 5762 pt's
- Pain at rest:
NNT 3.6

Apfel PAIN 2013

Reduced PONV

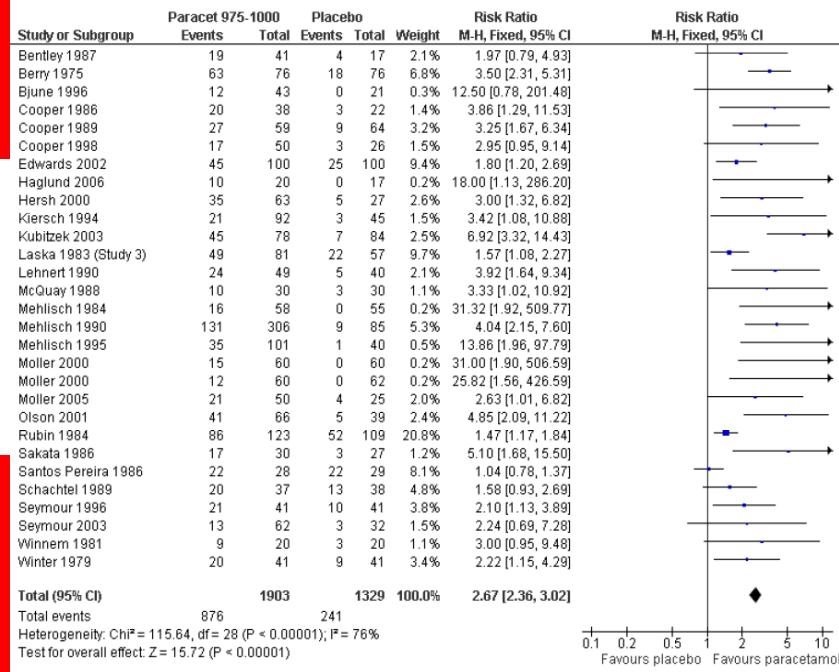
Paracetamol:
effective, safe
& cheap

Single dose oral paracetamol (acetaminophen) for postoperative pain in adults

2008 The Cochrane Collaboration

Terence Toms¹, Henry J McQuay¹, Sheena Derry¹, R Andrew Moore¹

Figure 3. Forest plot of comparison: 5 Paracetamol 975-1000 mg versus placebo, outcome: 5.1 Participants with at least 50% pain relief over 4 to 6 hours.



NSAIDs

Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review

60 randomized trials included

E. Maund*, C. McDaid, S. Rice, K. Wright, B. Jenkins and N. Woolacott

BJA 2011

Table 1 Pairwise comparisons for primary morphine-related outcomes. The first treatment is the intervention and the second is the control. A negative mean difference indicates that the intervention was more effective than the control treatment. An OR <1 indicates that the intervention has performed better than the control. *Adjusted for baseline morphine consumption

Comparison	Morphine consumption, unadjusted, mean difference, mg (95% CrI)	Morphine consumption, adjusted,* mean difference, mg (95% CrI)	Nausea and PONV, pairwise OR (95% CrI)	Sedation, pairwise OR (95% CrI)
Paracetamol vs placebo	-6.34 (-9.02, -3.65)	-8.68 (-11.43, -5.94)	1.00 (0.60, 1.53)	1.62 (0.32, 5.02)
NSAID vs placebo	-10.18 (-11.65, -8.72)	-9.45 (-10.90, -8.01)	0.70 (0.53, 0.88)	0.53 (0.20, 1.01)

- Opioid reduction 30 (- 50) %
- NNT 2-3
- Reduction of opioid related adverse effects

Systematic reviews and metaanalyses of single dose dexamethasone in POP

Perioperative Single Dose Systemic Dexamethasone for Postoperative Pain

A Meta-analysis of Randomized Controlled Trials

Anesthesiology, September 2011

Gildásio S. De Oliveira, Jr., M.D.,* Marcela D. Almeida, M.D.,† Honorio T. Benzon, M.D.,‡
Robert J. McCarthy, Pharm.D.§

24 RCTs & 2751 pt's

Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis

N. H. Waldron, C. A. Jones, T. J. Gan, T. K. Allen and A. S. Habib*

BJA Advance Access published December 5, 2012

45 RCTs & 5796 pt's

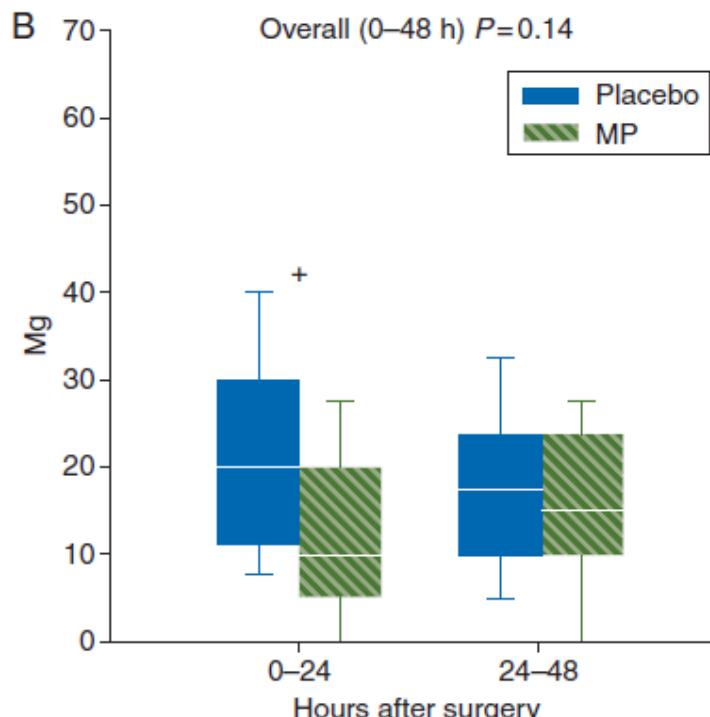
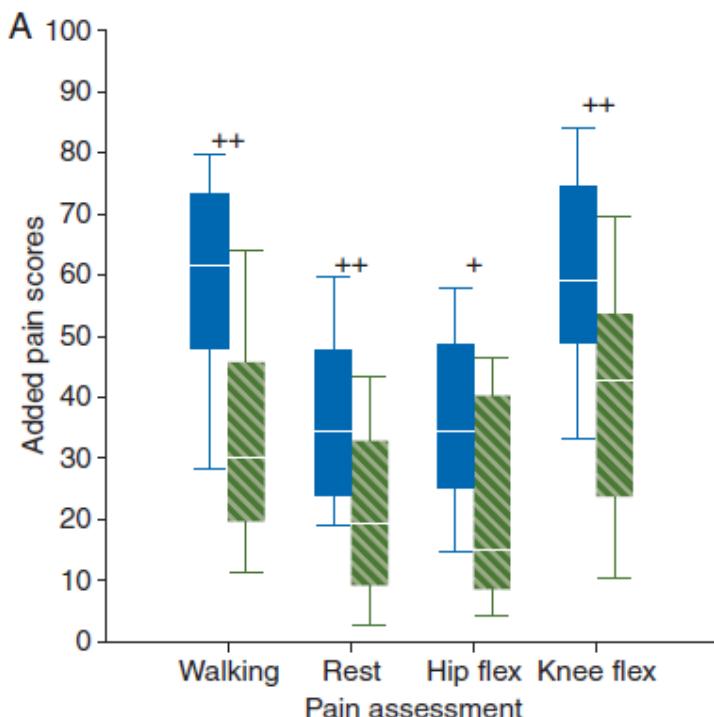
- Early and late pain + opioid consumption reduced
- Marginal effects
- OBS: mostly low dose use DEXA (4-8 mg)!

Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial

T. H. Lunn^{1,2*}, B. B. Kristensen^{1,2}, L. Ø. Andersen^{1,2}, H. Husted^{2,3}, K. S. Otte^{2,3}, L. Gaarn-Larsen^{1,2} and H. Kehlet^{2,4}

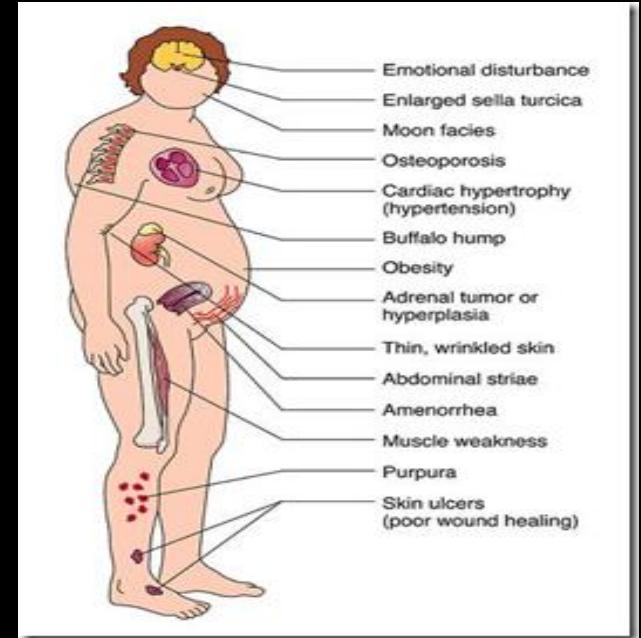
British Journal of Anaesthesia 106 (2): 230–8 (2011)

- 48 pt's: 125 mg methylprednisolone vs. placebo
- Multimodal POP: PCM+Celecoxib+Gabapentin
 - PONV + Zofran + CRP + fatigue reduced



What about side effects?

Well-known adverse effects
from long term GCC treatment



Side effects of single dose GCC?

- Waldron BJA 2012
 - 9 RCT & 1020 pt's: NS for late healing
 - 14 RCT & 1449 pt's: NS for infection

Intraoperative High-Dose Dexamethasone for Cardiac Surgery

A Randomized Controlled Trial

Jan M. Dieleman, MD

JAMA, November 7, 2012

RCT & blinded multicenter study / 4494 pt's
Dexamethasone 1 mg/ kg vs. placebo

Table 2. Primary Study End Point and Components of the Primary Study End Point in the Dexamethasone and Placebo Groups

	No. (%) of Patients		
	Dexamethasone (n = 2235)	Placebo (n = 2247)	Relative Risk (95% CI)
Primary study end point ^a	157 (7.0)	191 (8.5)	0.83 (0.67-1.01)
Components of the primary study end point			
Death	31 (1.4)	34 (1.5)	0.92 (0.57-1.49)
Myocardial infarction	35 (1.6)	39 (1.7)	0.90 (0.57-1.42)
Stroke	29 (1.3)	32 (1.4)	0.91 (0.55-1.50)
Renal failure	28 (1.3)	40 (1.8)	0.70 (0.44-1.14)
Respiratory failure	67 (3.0)	97 (4.3)	0.69 (0.51-0.94)

^aPrimary study end point was a composite of death, myocardial infarction, stroke, renal failure, or respiratory failure, within 30 days after surgery.

P < 0.07

Intraoperative High-Dose Dexamethasone for Cardiac Surgery

A Randomized Controlled Trial

Jan M. Dieleman, MD

JAMA, November 7, 2012

- Secondary outcome:
 - Reduction of
 - Respiratory problems & need for ventilator
 - Infection (!)
 - LOS at ICU & department
 - Kidney failure
- NB:
 - No outcome worsened !!
- 'Safety-studie' we needed!

Single dose GCC

- Dose – intermedium-large
- Reduced
 - Pain
 - PONV
 - Fatigue
 - Surgical stress response
- Potentially: ideal perioperative drug??

>99 RCT's in POP with gabapentin

Large variety of surgical procedures:

- Hysterectomy
- Orthopedics (THA, arthroscopy, ACL, Handsurgery, wounds, spine)
- Spinal surgery (lumbar disc, lumbar fusion)
- Mastectomy
- Lap. Chol.
- ENH (tonsillectomy, septumplastic)
- Thyroidectomy
- Neurosurgery (plexus brachialis, craniotomy)
- Nefrectomy
- Lap. Gyn.
- Hernie inguinalis
- Various (Litotomy, varicocele, thoracotomy, CABG, keratotomy, sectio)

Systematic reviews 2006-2007

(Ho, PAIN 2006; Tiippana A&A 2007, Peng, Pain Res Manage 2007, Mathiesen, BMC Anesthesiol 2007)

- N= 16-23 RCT (1100-1900 pts)
- Morfin reduction: 14-32 mg/24h
- VAS-pain reduced (rest + mobilisation)
- Opioid related side-effects:
 - Vomiting (NNT 6-8)
 - Itching (RR 0.3)
 - Nausea (NNT 7-25)
 - Urinary retention (NNT 7)
- Increased risc of:
 - Sedation (NNH 35)
 - Dizziness (NS 12)

Gabapentin Improves Postcesarean Delivery Pain Management: A Randomized, Placebo-Controlled Trial

Albert Moore, MD,* Joseph Costello, MD,* Paul Wieczorek, MD,* Vibhuti Shah, MD,†

Anna Taddio, PhD,§ and Jose C. A. Carvalho, MD, PhD*‡

Anesht Analg 2011

Table 2. Incidence of Maternal Adverse Reactions During the First 48 Postoperative Hours

	Gabapentin group (n = 21)	Placebo group (n = 23)	P value
Nausea	12 (57)	8 (34)	0.14
Severe nausea	2 (9)	0 (0)	0.22
Vomiting	5 (24)	3 (13)	0.35
Severe vomiting	1 (5)	0 (0)	0.47
Pruritus	16 (76)	22 (96)	0.09
Severe pruritus	2 (10)	4 (17)	0.66
Sedation	17 (81)	17 (74)	0.58
Severe sedation	4 (19)	0 (0)	0.04



Clinical relevance ??

What about pregabalin?

Efficacy of pregabalin in acute postoperative pain: a meta-analysis

11 RCT

J. Zhang¹, K.-Y. Ho^{2*} and Y. Wang¹

BJA Advance Access published February 26, 2011

Efficacy and safety of perioperative pregabalin for post-operative pain: a meta-analysis of randomized-controlled trials

18 RCT

E. ENGELMAN and F. CATELOY
Department of Anaesthesia, CUB Hopital Erasme, Brussels, Belgium

ACTA 2011

BJA Advance Access published September 10, 2014

British Journal of Anaesthesia Page 1 of 22
doi:10.1093/bja/aeu293

BJA

Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis

55 RCT

B. M. Mishriky, N. H. Waldron and A. S. Habib*

Overall picture - PREGABALIN:

- Reduced
 - Pain at rest and mobilization
 - 24h morphine consumption
 - Opioid related adverse effects
- Side-effects like gabapentin
- BUT high risk for visual disturbances

CONCLUSION (for now): Use **GABAPENTIN**

Peripheral nerveblock



- Superior analgesia
- OBS:
 - Succés ratio
 - Motor pareses
 - Duration – ward pain at night..?
 - Exces rebound pain?

Macfarlane: Clin Orthop Relat Res 2009

Ilfeld: Anesthesiology 2008

What do we know?

Post-operative analgesic effects of paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review

J. B. DAHL, R. V. NIELSEN, J. WETTERSLEV, L. NIKOLAJSEN, K. HAMUNEN, V. K. KONTINEN, M. S. HANSEN,
J. J. KJER and O. MATHIESEN; SCANDINAVIAN POSTOPERATIVE PAIN ALLIANCE (SCAPALLI)

Department of Anaesthesia 4231, Centre of Head and Orthopaedics, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Adverse effects of perioperative paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review

O. MATHIESEN¹, J. WETTERSLEV², V. K. KONTINEN³, H.-C. POMMERGAARD⁴, L. NIKOLAJSEN⁵, J. ROSENBERG⁴,
M. S. HANSEN⁶, K. HAMUNEN⁷, J. J. KJER⁸, J. B. DAHL⁶ and SCANDINAVIAN POSTOPERATIVE PAIN ALLIANCE
(SCAPALLI)

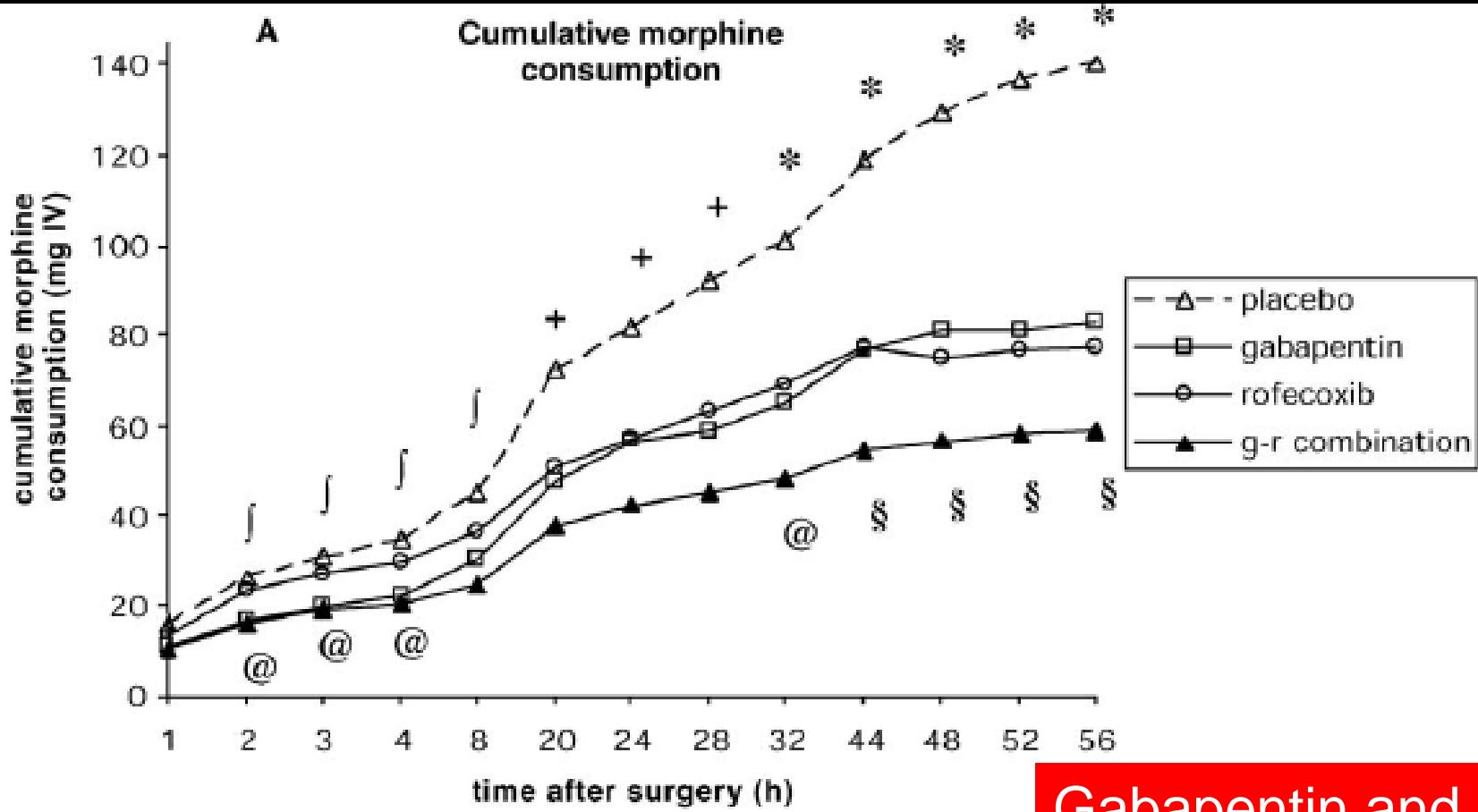
Paracetamol + NSAID for POP

- Hyllested BJA 2002 + Rømsing BJA 2002:
 - PCM + NSAID > PCM
 - PCM + NSAID may be > NSAID
- Ong A&A 2010:
 - 21 RCT's with 1909 pt'er
 - PCM + NSAID > PCM (17 of 20 RCT)
 - PCM + NSAID > NSAID (9 of 14 RCT)
 - PCM + NSAID: 30-40% better pain relief & reduced analgetic consumption compared to PCM or NSAID alone

A placebo-controlled randomized clinical trial of perioperative administration of gabapentin, rofecoxib and their combination for spontaneous and movement-evoked pain after abdominal hysterectomy

Ian Gilron^{a,*}, Elizabeth Orr^b, Dongsheng Tu^c, J. Peter O'Neill^d,
Jorge E. Zamora^e, Allan C. Bell^f

PAIN



Gabapentin and other analgesics ?

Opioid-sparing pain treatment

Analgesic	Opioid-sparing
Paracetamol	~ 20%
NSAID	~ 30%
Ketamine	~ 15%
Dextromethorphan	< 10%

Lack of good evidence for additive effect
of more than 2 (3?) drugs

Urgent need for large RCTs

Infiltrationsanæstesi

> 40%

Multimodal

Paracetamol + NSAID > 30%

Paracetamol + NSAID + gabapentin > 35%

+, +, +???

> ??%

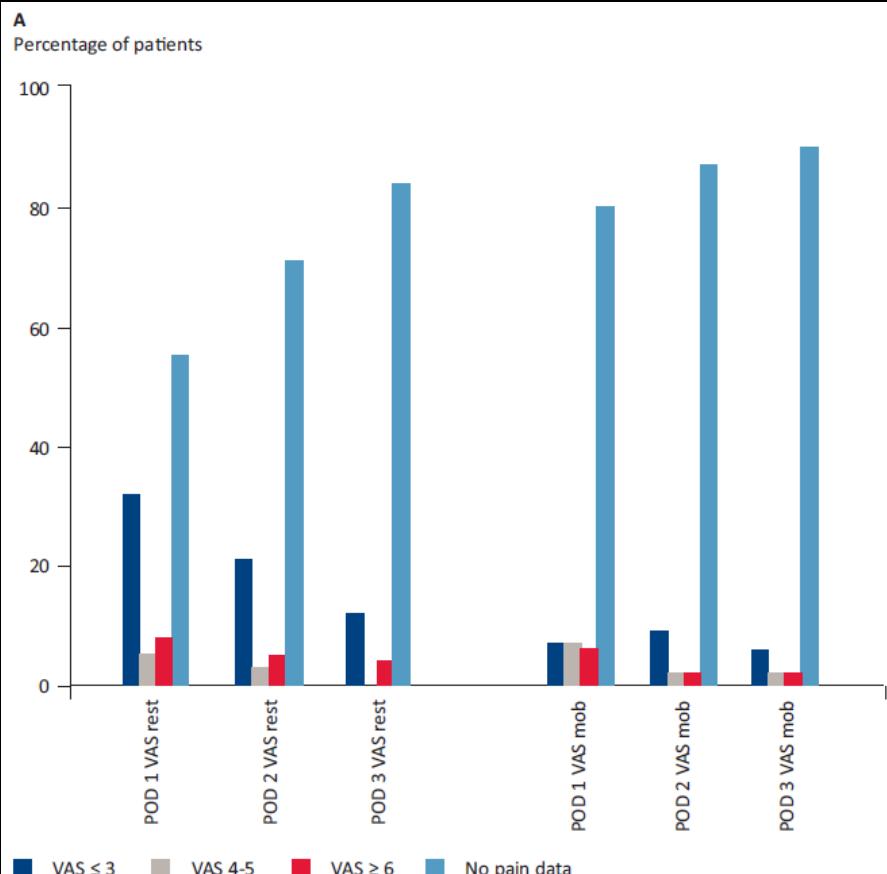
Need for improved treatment of postoperative pain

Ole Mathiesen¹, Berit Ahlmann Thomsen¹, Birgitte Kitter¹, Jørgen Berg Dahl² & Henrik Kehlet³

Dan Med J 59/4

April 2012

Cross sectional study - 121 patients
at 1100 bed University Hospital



■ TABLE 2

Percentage of pa-tients who received basic non-opioid analgesic treatment.

Treatment

Paracetamol	97
Paracetamol + NSAID	44
Paracetamol + gabapentin	12
Paracetamol + NSAID + gabapentin	7

NSAID = non-steroidal anti-inflammatory drug.

■ TABLE 3

Percentage of pa-tients with nausea on the first three postoperative days.

	Nausea	POD 1	POD 2	POD 3
Yes	23	18	20	
No	75	58	52	
No data	2	24	28	

POD = postoperative day.

Guidelines for the staff:
PONV: 7%
Pain : 14%

Quality Assurance investigation: 1 week patient data from orthopedic ward

- EPM not checked in the morning
- Medication not given
- Double prescriptions
- Old prescriptions not deleted
- No plan for POP at PACU
- Morphine doses not adjusted
- EPI-bolus not used, instead morphine
- Etc, Etc

What are we facing?

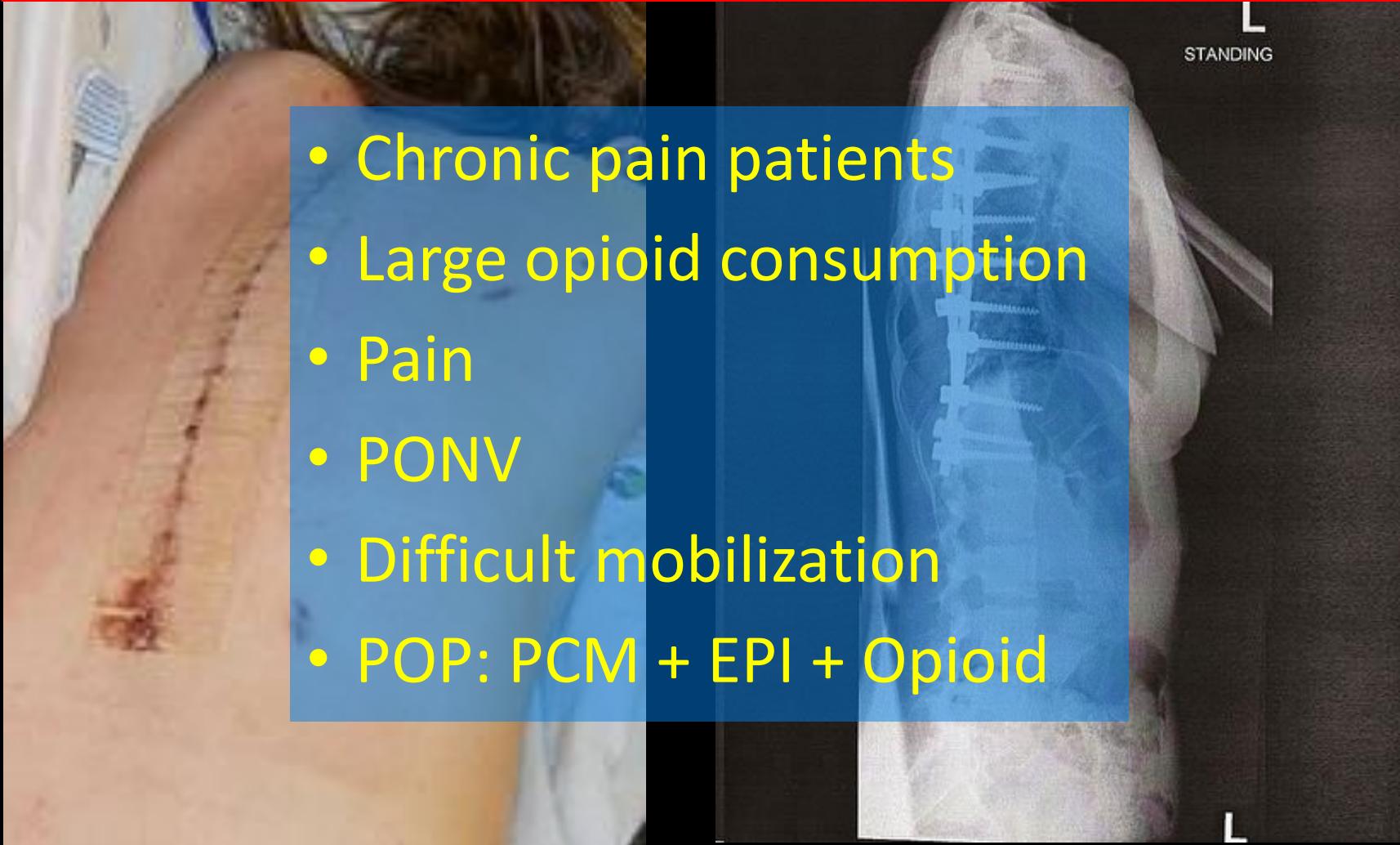
- Randomness & lack of common goals
- Guided by local traditions and individual not-documented preferences
- Logistical challenges related to IT-systems
- Lack of documentation

What should we do?

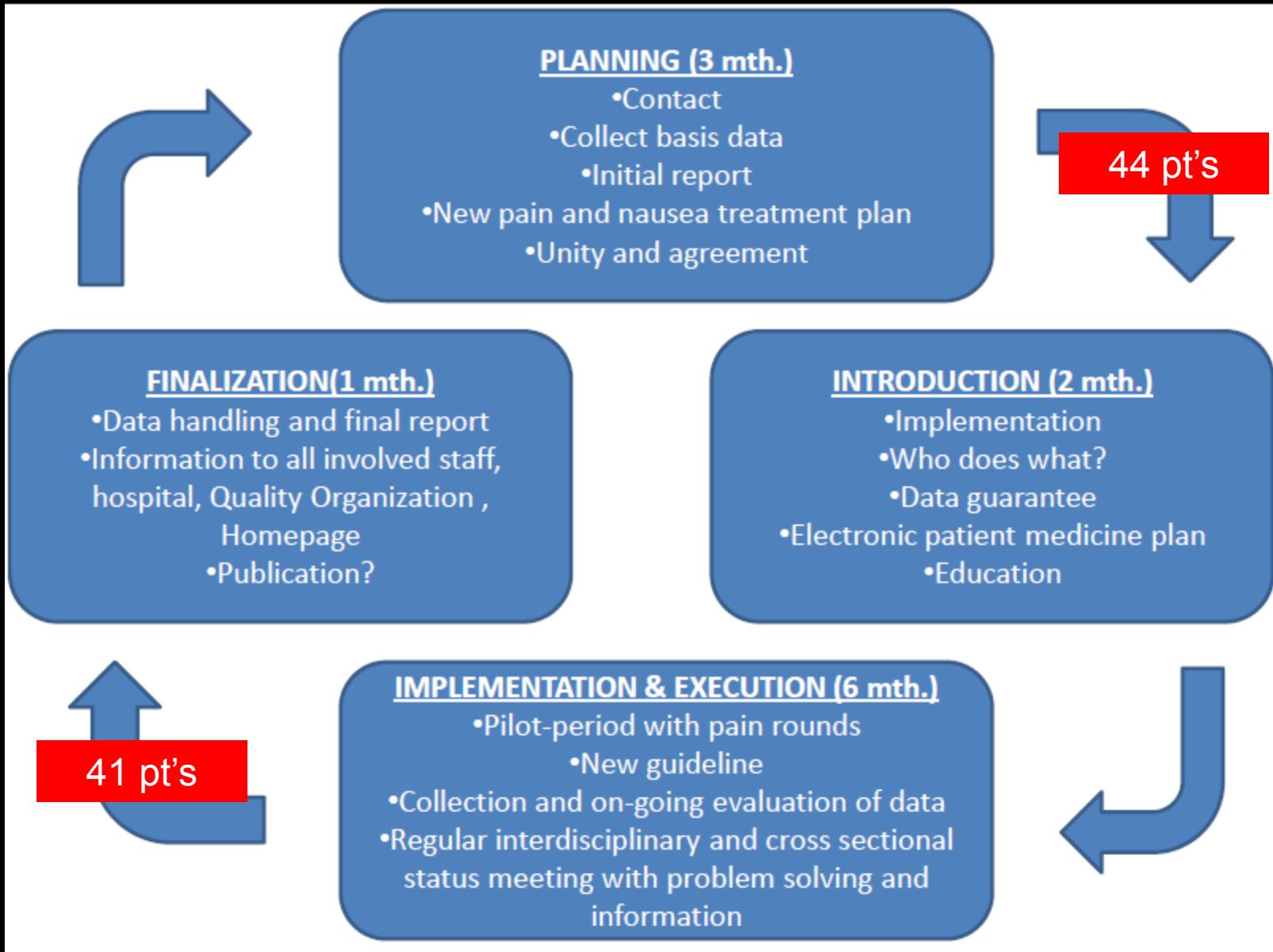
- Pain treatment guidelines - covering the patient course fra A to Z – 90% of patients
- Interdisciplinary collaboration
- Organizational changes/effort
- A coordinating project unit (APS..)
- Key words:
 - Implementation
 - Documentation
 - Teaching

Exampel from EAS-project at Rigshospitalet: Optimization of POP in multi-level instrumentation spine surgery

- Chronic pain patients
- Large opioid consumption
- Pain
- PONV
- Difficult mobilization
- POP: PCM + EPI + Opioid



Work method



Major spine surgery > 3 levels of instrumentation

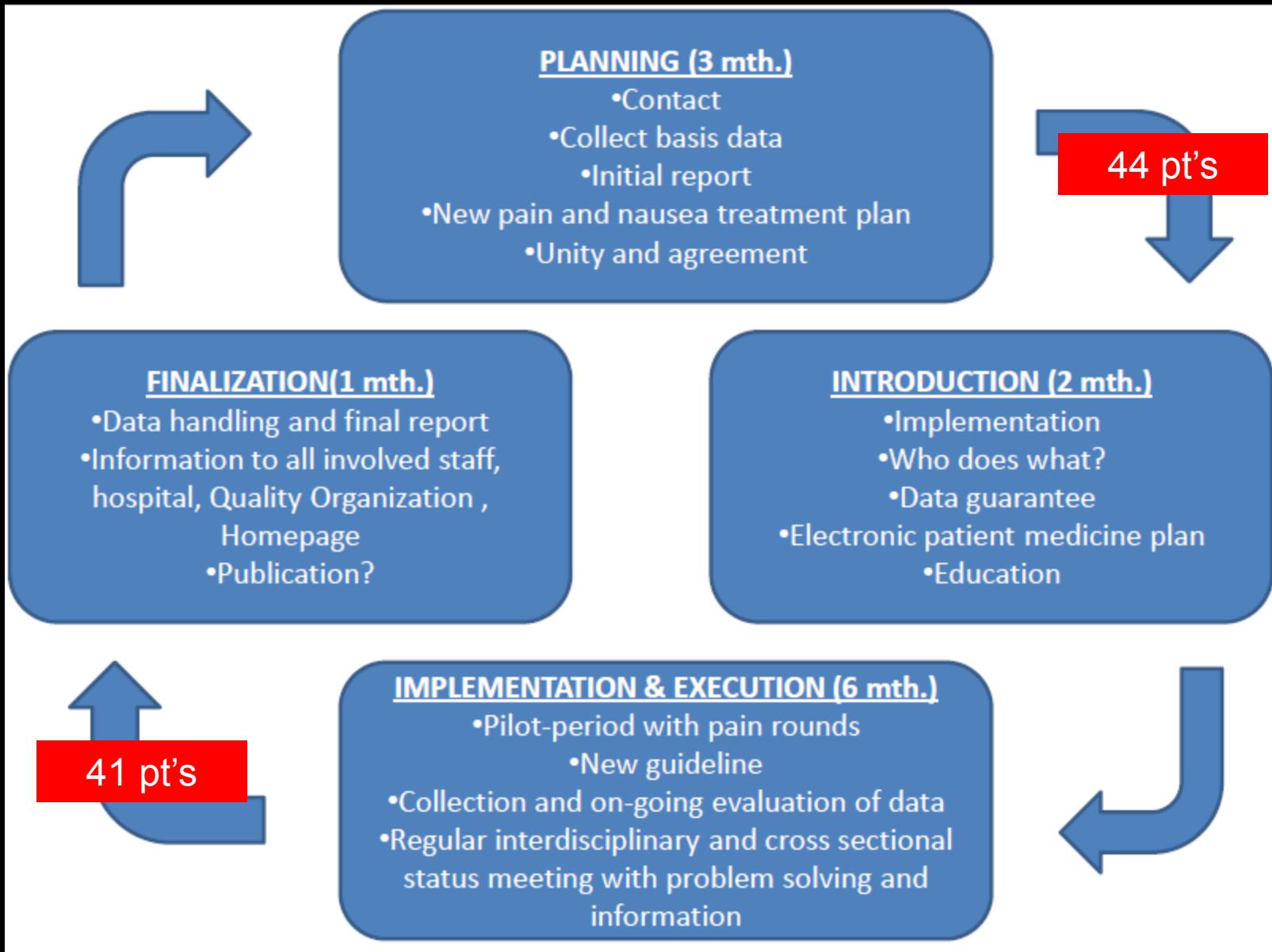
Pre-operative	<ul style="list-style-type: none">• Paracetamol R 2 g• Gabapentin 900 mg• Celecoxib 400 mg
Peri-operative	<ul style="list-style-type: none">• Dexamethasone 24 mg• Ketamin – low-dose• Propofol / remifentanil• Epidural• Morphine• Ondansetron
Post-operative	<ul style="list-style-type: none">• Paracetamol• Ibuprofen• Gabapentin• Epidural
Pain?	<ol style="list-style-type: none">1. Morphine2. Chlorzoxazone3. Increase gabapentin
PONV	<ol style="list-style-type: none">1. Ondansetron, DHB, Dexamethasone

SMERTEPLAN FOR ELEKTIV NON-MALIGN RYGKIRURGI PÅ MERE END 3 NIVEAUER

PRÆ-OPERATIVT						
Vanligt opioid						
Pamol R	tbl		2 g.			
Gabapentin	tbl		900 mg			
Celebra	tbl		400 mg			
PER-OPERATIVT						
Dexametason	iv		24 mg			
S-ketamin	iv-bolus		0,5 mg/kg			
S-ketamin	inf.		0,3 mg/kg/t	(stop 45 min før slut op)		
Propofol	inf.					
Ultiva	inf.					
Zofran	iv		4 mg	v/afslutning af anæstesi		
(45 min før op slut:)						
Morfín	iv	0,3 mg/kg		Vanlig højdosis opioid >100 mg peroral		
Fentanyl	iv		0,05 mg PN	Morfín iv	0,4 mg/kg	
				v/smertegennembrud efter slut AN		
EPI	1. Valg		PCA & LA	2. Valg		
Lidokain 2% m/adr	Test dosis	3 ml	PCA-morfín	inf		1 mg/t
Bupivakain 1/4 %	Bolus	10 ml	Bupivakain 1/4%	Infiltrations anæstesi		40-60 ml
POST-OPERATIVT						
0. Døgn						
Vanligt opioid						
Pamol	tbl	1 g x 2				
Morfín	iv	PN 2,5-10 mg	Morfín	tbl		PN 10-30 m
Bupivakain 1/4 % m/Morfín	inf i epi	5 ml/t	PCA-morfín	inf 1mg/t + bolus 2 mg/bolus		
Vanlig højdosis opioid >100 mg peroral						
Lav-dosis S-ketamin		inf		0,03 mg/kg/t		
Morfín	iv	PN 10-20 mg	Morfín	tbl		PN 30-60 m
1. Døgn						
Vanligt opioid						
Pamol	tbl	1 g x 4				
Ibrufen	tbl	400 mg x 4				
Gabapentin	tbl	400 mg + 600 mg				
Morfín	iv	PN 2,5-10 mg	Morfín	tbl		PN 10-30 m
Bupivakain 1/4 % m/Morfín	inf i epi	5 ml/t	PCA-morfín	inf 1mg/t + bolus 2 mg/bolus		
Vanlig højdosis opioid >100 mg peroral						
Lav-dosis S-ketamin		inf		0,03 mg/kg/t		
Morfín	iv	PN 10-20 mg	Morfín	tbl		PN 30-60 m
2. Døgn						
Vanligt opioid						
Pamol	tbl	1 g x 4				
Ibrufen	tbl	400 mg x 4				
Gabapentin	tbl	400 mg + 600 mg				
Morfín	iv	PN 2,5-10 mg	Morfín	tbl		PN 10-30 m
Bupivakain 1/4 % m/Morfín	inf i epi	5 ml/t	PCA-morfín	sep		KI 10.00
			Contalgin	tbl		20 mg x 2
Vanlig højdosis opioid >100 mg peroral						
Lav-dosis S-ketamin		inf		0,03 mg/kg/t		
Morfín	iv	PN 10-20 mg	Morfín	tbl		PN 30-60 m
3. Døgn						
Vanligt opioid						
Pamol	tbl	1 g x 4				
Ibrufen	tbl	400 mg x 4				
Gabapentin	tbl	400 mg + 600 mg				
Morfín	iv	PN 2,5-10 mg	Morfín	tbl		PN 10-30 m
Bupivakain 1/4 % m/Morfín	inf i epi	5 ml/t	Etter PCA			
			Contalgin	tbl		20 mg x 2
Vanlig højdosis opioid >100 mg peroral						
Lav-dosis S-ketamin		sep		KI 10.00		
Morfín	iv	PN 10-20 mg	Morfín	tbl		PN 30-60 m

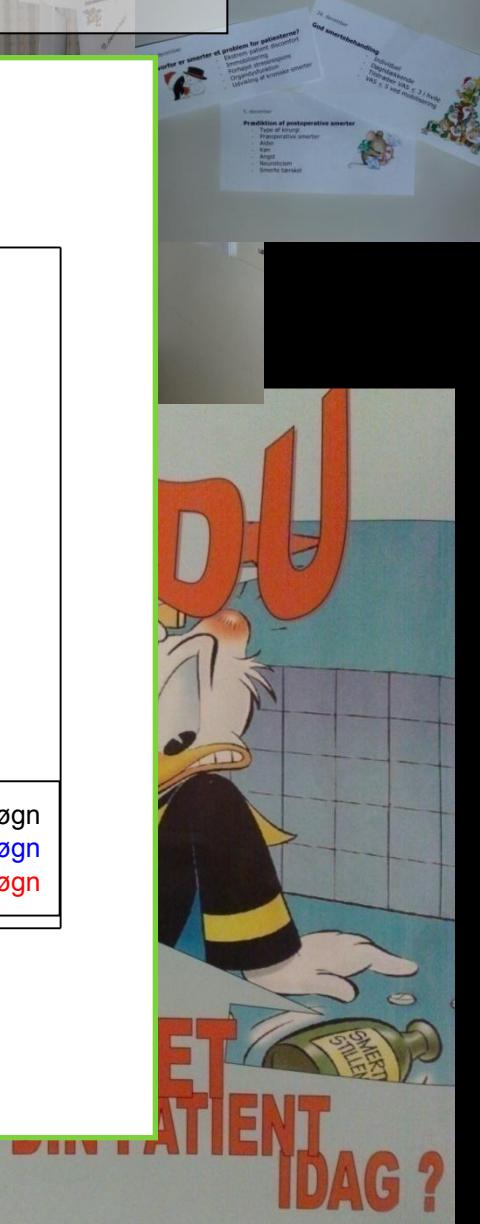
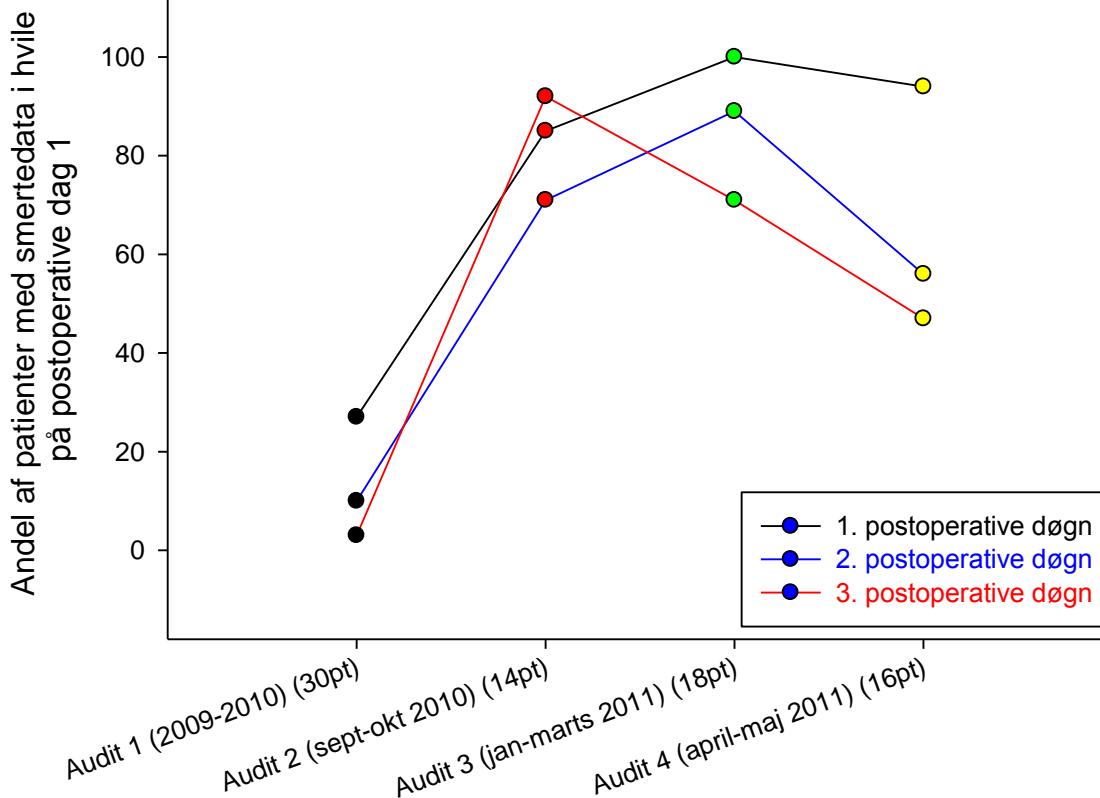
SMERTEFRIAN FOR EFFEKTIV NON-MAIIGN RYGKURBING PÅ MERE END 3 NIVEAUER

Work method



Pain-score-project

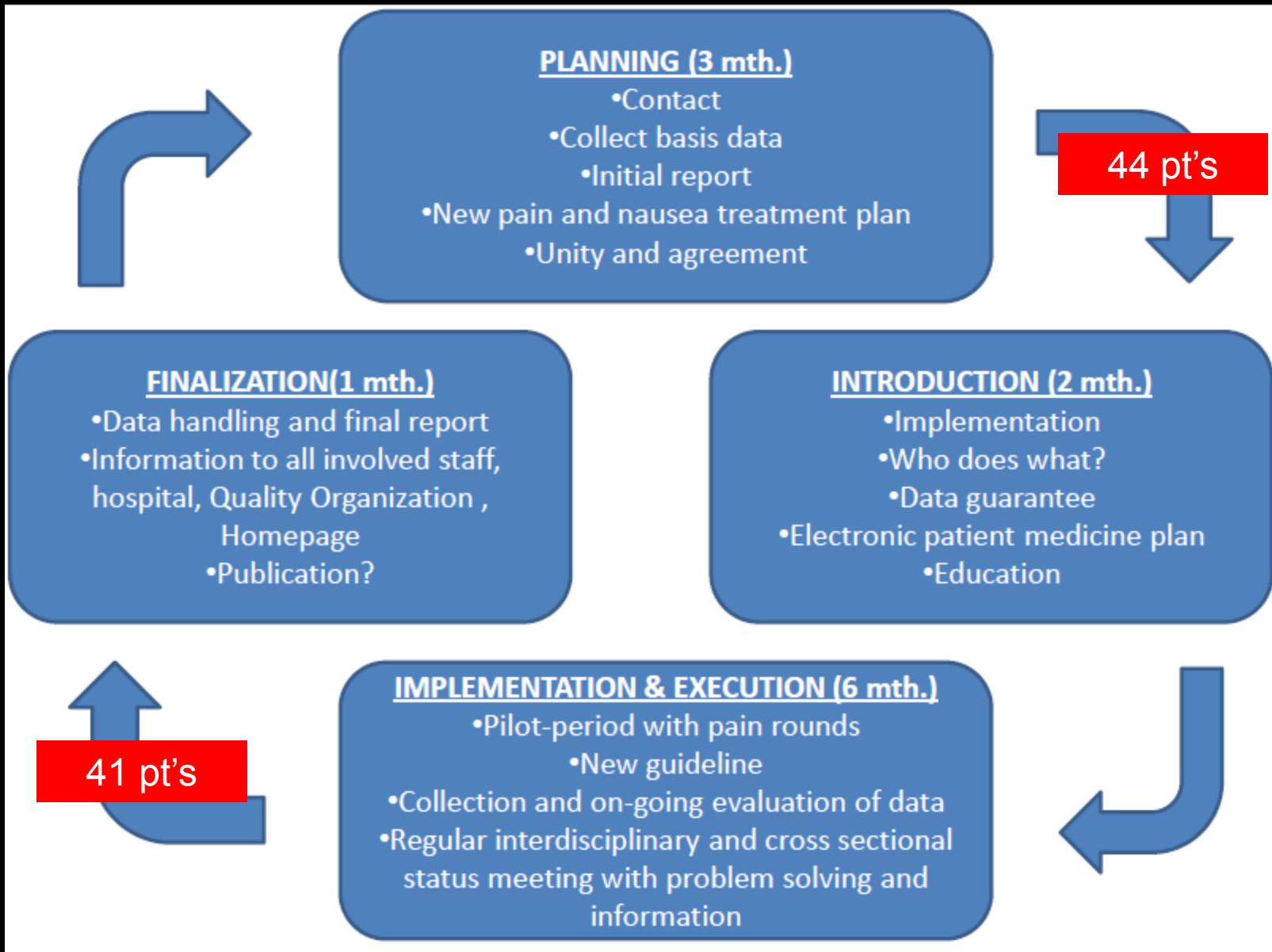
HAR
DU
VAS-SKO
DIN PATIENT
?



Status group

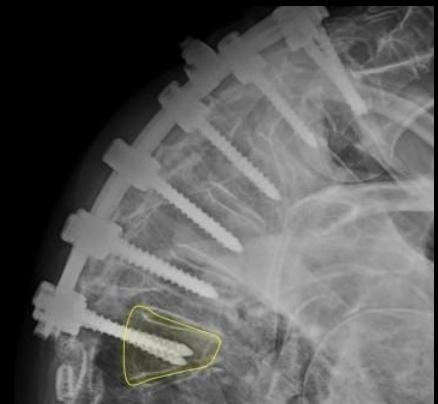
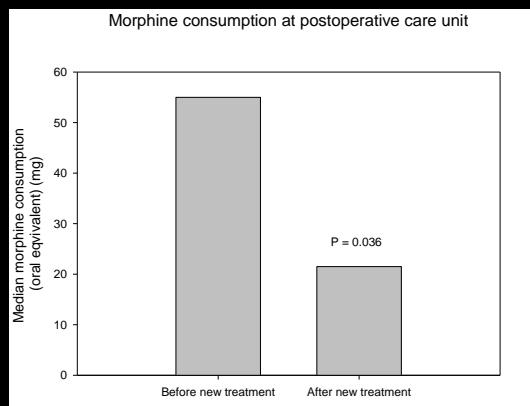
- All involved staff of the course of the patient
 - Anaesthesia (nurse / doctor)
 - PACU
 - Surgeon
 - Ward staff
 - Physiotherapist
 - Acute Pain Unit – project koordinator and lead
 - Quality koordinator
- Regular meeting every (2-)4 weeks
- Problems – information - planning

Work method

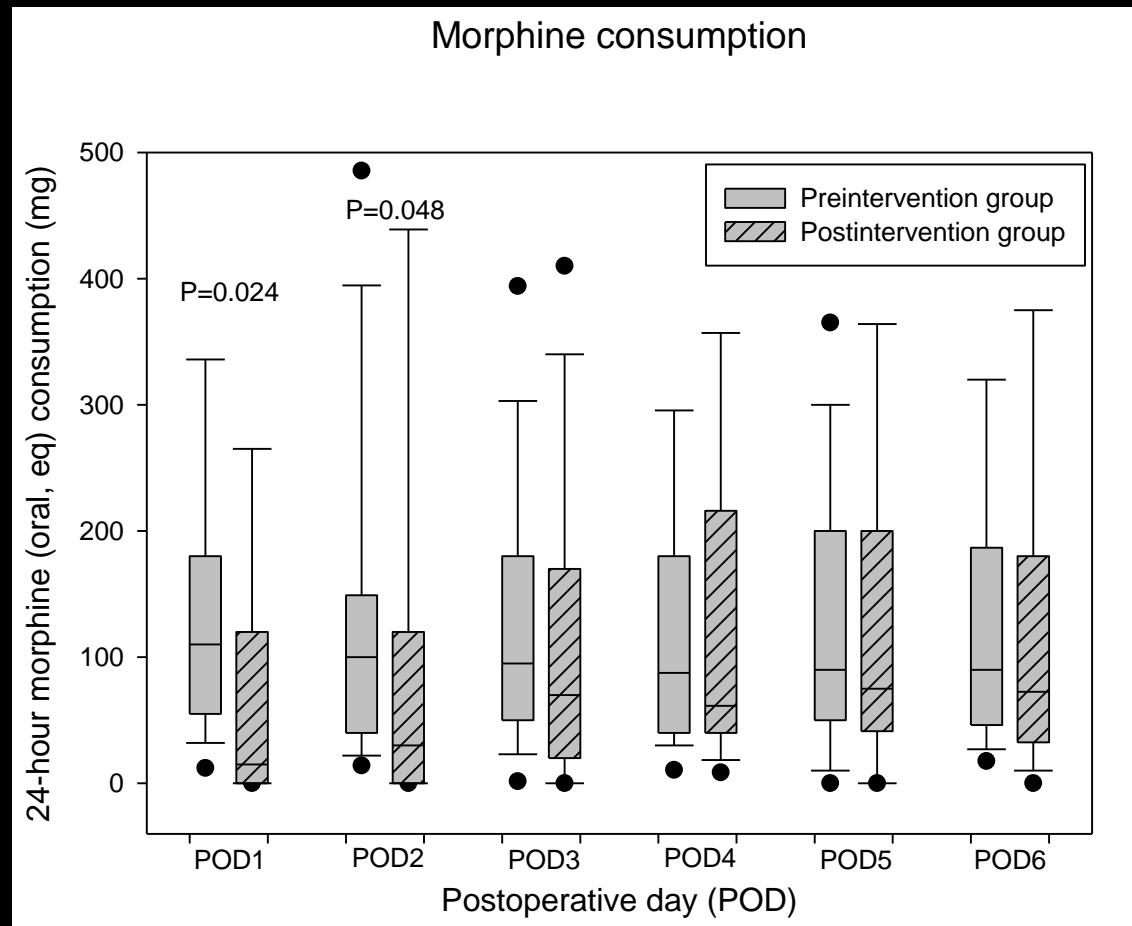


Results

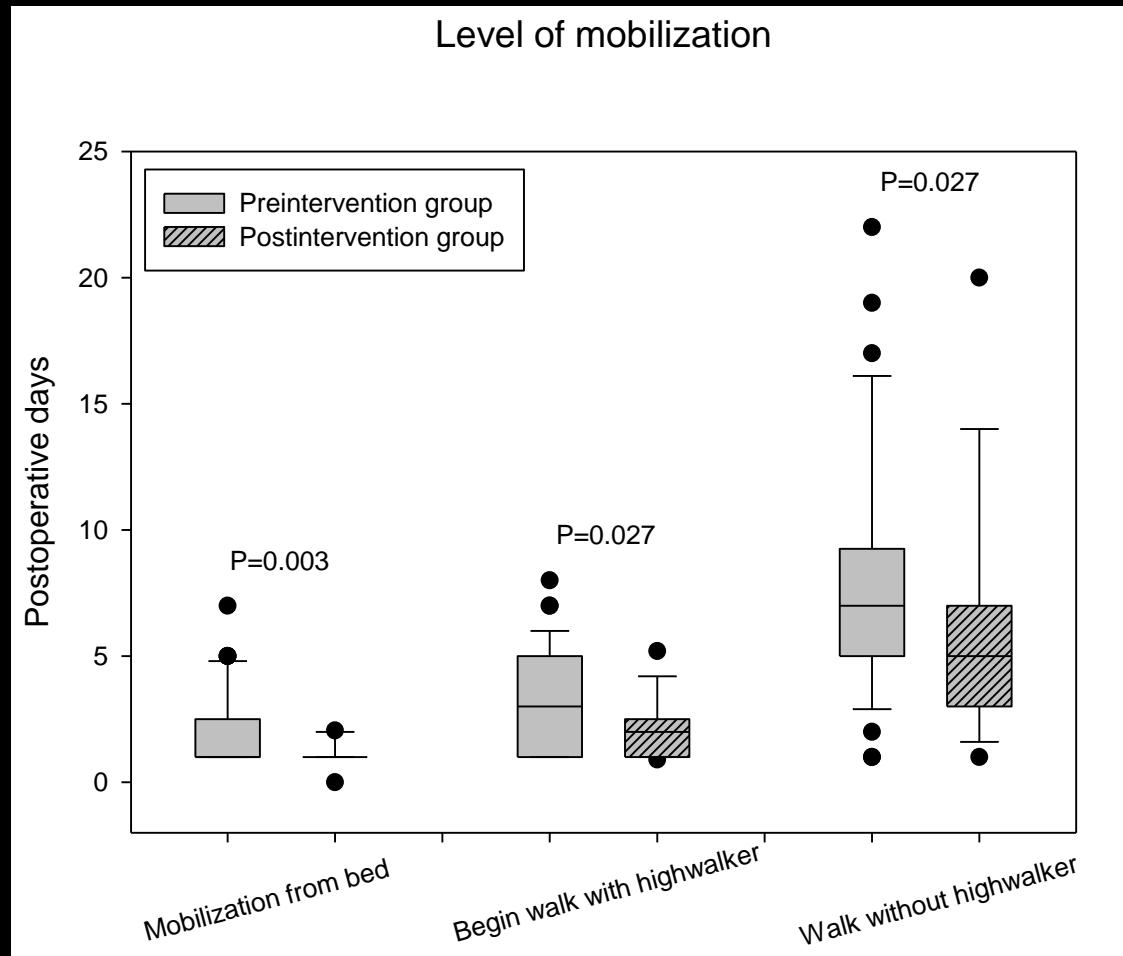
- (Cohorte study with historic control group)
- PACU
 - Maximal pain levels reduced
 - Morphine consumption reduced
 - LOS at PACU reduced with 1 h (18%)



Morphine on POD 1-6



Mobilization



Length of stay
reduced from
median (range):
9 (3-29) to
7 (3-22) days

One year....!

Basic recipé for postoperative pain treatment

- Analgesic elements:
 1. Paracetamol (1g x 4)
 2. NSAID: Ibuprofen (400 mg x 4) (max: 3-5 days)
 3. Dexamethasone (single dose 16 mg)
 4. Gabapentin (single dose: 600-900 mg)
- Local anaesthetics (infiltration/bloks/EPI)
- Morphine as escape
- Organizational approach & implementation
- Guidelines, cross-sectional collaboration