Anesthetic Considerations for Patients with Chronic Pain

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Disclosures

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What are the issues?

- What are the common pain medications employed in chronic pain patients?
- Are there important pharmacogenetic considerations?
- Is the chronic pain patient predisposed to increased postoperative pain?
- In general, how should postoperative pain be managed?
- How should postoperative opioids, in either the opioid tolerant or opioid abusing patient, be managed?

Perioperative Management of Chronic Pain Patient

- What are the common pain medications employed in chronic pain patients and what are their anesthetic implications?

Preoperative Management: Common Drugs

- **NSAID's**
- **Opioids including tramadol**
- **Psychotropic:**
  - **TCA's: amitriptyline/nortriptyline**
  - **SSRI's: Fluoxitene, paroxitene, sertraline, citalopram, escitalopram**
  - **SNRI's: Duloxitene, venlafaxine**
  - **MAOI's: Uncommon**
- **Anticonvulsants: gabapentin, pregabalin, valproic acid, topiramate**
- **Benzodiazepines**
- **α-2 Agonists: Clonidine**

Perioperative Bleeding

- NSAID's
- Valproic Acid (CYP2C9/10 effect of valproate) leads to increased effects of NSAID's and warfarin
- NSAID's and SSRI's (inhibit serotonin reuptake of platelets)
- Warfarin and SSRI's/SNRI's (decrease warfarin metabolism)
- Topiramate and Warfarin (Lowers warfarin metabolism via CYP3A4)

MAO Inhibitors

- No TCA’s for at least 14 days
- No SSRI’s for 14 days or 35 days for fluoxitene
- Fentanyl and meperidine can cause serotonin syndrome

Perioperative Management of Chronic Pain Patient

- Are there important pharmacogenetic considerations?

Mu-receptor Polymorphism: A118G

Table 2

Genotype frequency, demand and consumed morphine dose in milligrams for the patients who received patient-controlled analgesia alone.

	Genotype frequency (%)	Demand in first 24 h	Demand in second 24 h	Demand in first 48 h	Dose in first 24 h	Dose in first 48 h
AA	62	24.3 (15.4)	9.5 (9.4)	39.0 (24.7)	16.0 (8.0)	25.3 (15.5)
GG	11	36.1 (15.2)	18.3 (14.9)	57.8 (24.7)	22.3 (10.0)	40.4 (22.1)
AG	27	22.2 (14.6)	10.5 (8.5)	35.3 (23.3)	14.8 (7.1)	25.6 (11.7)
AA vs. GG		$^*P = 0.033$	$^*P = 0.028$	$^*P = 0.026$	$^*P = 0.018$	$^*P = 0.003$
GG vs. AG		$^*P = 0.021$	$P = 0.059$	$^*P = 0.012$	$^*P = 0.010$	$^*P = 0.008$

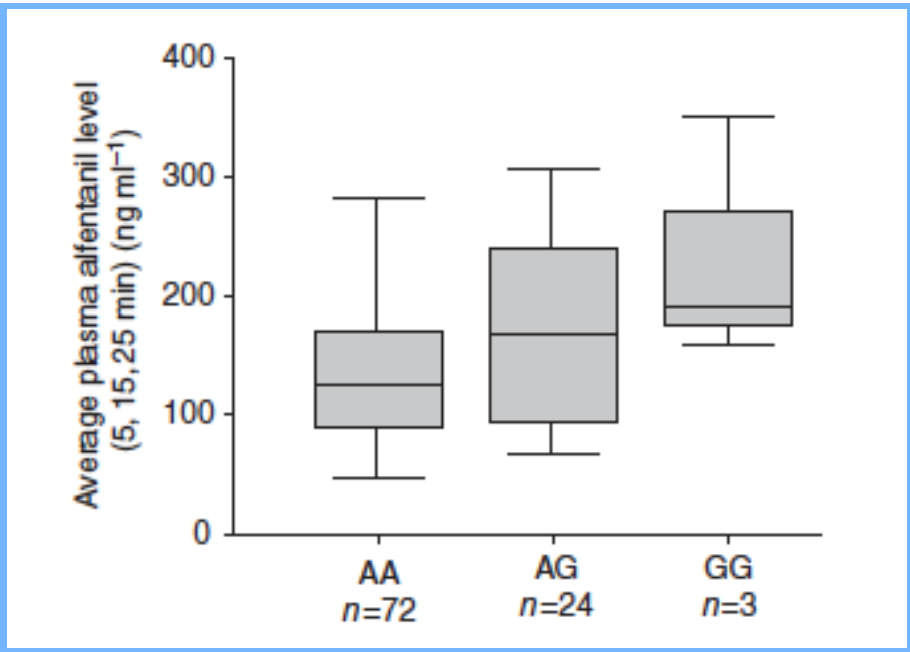
AA, wild-type homozygous; AG, mutant heterozygous; GG, mutant homozygous.
The morphine consumed doses are expressed as mean (standard deviation).
Demand is the dose that represents the number of times the patient pushed the release button of the patient-controlled analgesia device.
P-value for one-way analysis of variance (ANOVA) with *post hoc* tests ($^*P < 0.05$).

W.Y. CHOU, et al. Acta Anaesthesiol Scand 2006; 50: 787–792 Total knee arthroplasty
(Similar to study of TAH in Anesthesiology 2006;105:334-337)

Mu-receptor Polymorphism: A118G

Table 2 Analgesic endpoints compared between wild-type (AA) and A118G SNP mutations (AG/GG)

	AA (n=72)	AG/GG (n=27)	
Dose (over 25 min) (μg)	4060 (3030)	6271 (4677)	P=0.009
Dose (over 25 min)/wt (μg kg^{-1})	51.4 (37.3)	75.4 (44.9)	P=0.004
Dose (over 25 min)/wt/RIP (μg kg^{-1} kV^{-1})	0.0011 (0.0009)	0.0017 (0.001)	P=0.002
Boluses attempted (over 25 min)	3.4 (3.4)	7.2 (5.9)	P=0.015
Boluses successful (over 25 min)	1.9 (1.0)	3.4 (2.6)	P=0.013
Boluses failed (over 25 min)	1.5 (2.9)	3.8 (4.6)	P=0.042
Mean plasma alfentanil concentration (over 25 min) (ng ml^{-1})	139 (68)	177 (82)	P=0.034
Mean VAS pain score (over 25 min) (0–100)	2.1 (1.6)	3.2 (1.9)	P=0.047



Y. Ginosar Br J Anaesth 2009; 103: 420–7 Alfentanil and ESWL

Significance of A118G SNP

- Might G118G homozygotes be less sensitive to the analgesic effects of mu-opioids?
- Might G118G homozygotes have reduced nausea and vomiting with opioids?

Pharmacogenetic Interactions

- UGT (Uridine glycosyl transferase):
  - ❿ morphine*(active M-6-G)
  - ❿ hydromorphone*(HM-3-G, neuroexcitatory)
- ★There are essentially no clinically relevant interactions with other drugs used in chronic pain patients
- ★Metabolites, however, require normal renal function for clearance

* primary metabolic pathway

Pharmacogenetic Interactions

- Hepatic P450 Alleles:
  - **3A4**: fentanyl[s]*, methadone*, morphine, hydromorphone, hydrocodone, midazolam
  - **2D6**: codeine*, tramadol*, oxycodone*, hydrocodone*, methadone, fluoxitene*(also other SSRI'S), duloxetine*, amitriptyline*
  - **2C9**: NSAID's*, sertraline*
  - **2C19**: diazepam*
- Inhibitors :
  - **2C9/19**: fluoxitene
  - **2D6**: SSRI's(strong to weak), duloxetine(moderate)
  - **3A4**: fluoxitene and sertraline(weak)

* primary metabolic pathway

Pharmacogenetic Interactions

- Hepatic P450 Alleles:
  - 3A4: fentanyl[s]*, methadone*, morphine, hydromorphone, hydrocodone, midazolam
- Inhibitors :
  - Fluoxitene and sertraline (weak)
  - Up to 40% more active in women v. men

* primary metabolic pathway

Pharmacogenetic Interactions

- Hepatic P450 Alleles:
  - 2C9: NSAID's*, sertraline*
  - 2C19: diazepam*
- Inhibitors :
  - 2C9/19: fluoxitene
  - 2C9*3 Allele slow NSAID metabolism
  - 2C19*G681A Allele slow diazepam metabolism

* primary metabolic pathway

Pharmacogenetic Interactions

- Hepatic P450 Alleles:
  - **2D6**: codeine*, tramadol*, oxycodone*, hydrocodone*, methadone, fluoxitene*(also other SSRI'S), duloxetine*, amitriptyline*
- Inhibitors :
  - Many drugs compete for **2D6**;
  - 2-8% of population has reduced or absent **2D6**
  - Codeine is only true prodrug; needs conversion to morphine
  - Oxycodone and hydrocodone are analgesic but metabolize to oxymorphone and hydromorphone, both more potent
  - SSRI's(strong to weak), duloxetine(moderate)
  - Methadone (minor pathway) can accumulate

*primary metabolic pathway

Perioperative Management of Chronic Pain Patient

- How should postoperative pain be managed in patients with chronic pain?

Postoperative Pain Management

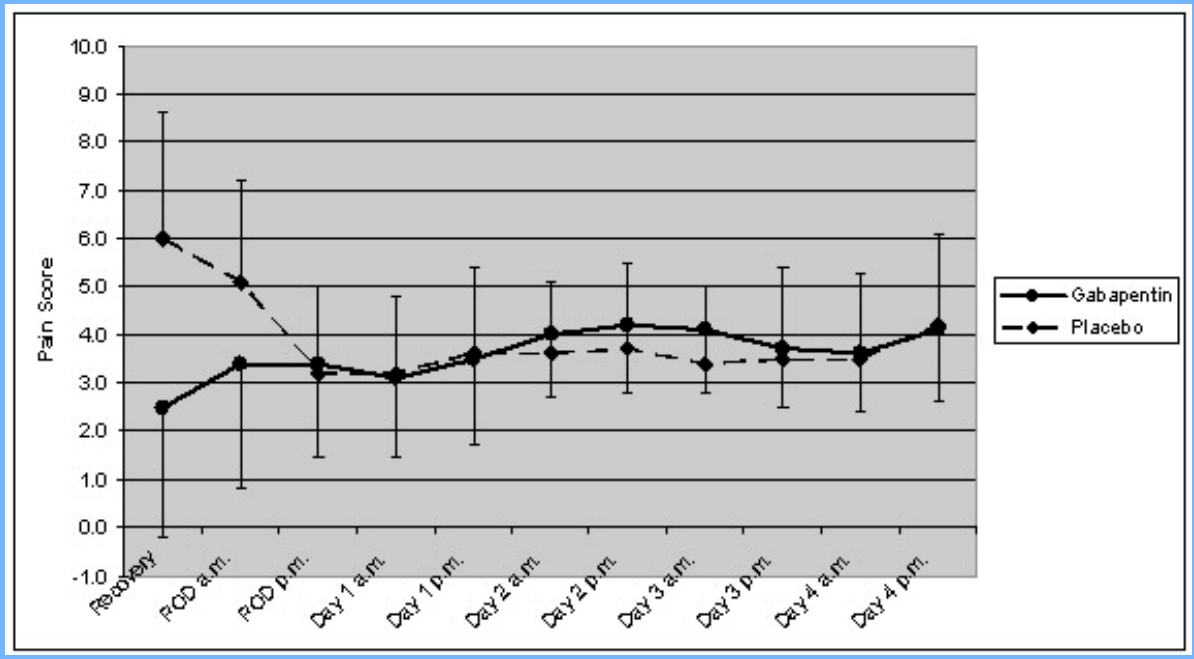
- Continue various psychotropic medications as soon as patients are able to take them!!
- AVOID tramadol, codeine, methadone in 2D6 blockade
- Adjust dosing as needed for oxycodone and hydrocodone in 2D6 blockade
- Administration of fluoxitene can lead to NSAID toxicity (or improved analgesia!)
- SSRI’s can lead to delayed metabolism of intraoperative opioids
- Women may need higher doses of commonly used analgesics (more 3A4), even though they are more tolerant of pain,!

Preoperative Neuromodulation

- Is there a role for preoperative administration of gabapentin?

Perioperative Gabapentin

Figure 1. Postoperative Pain scores. Data are shown as mean (SD).

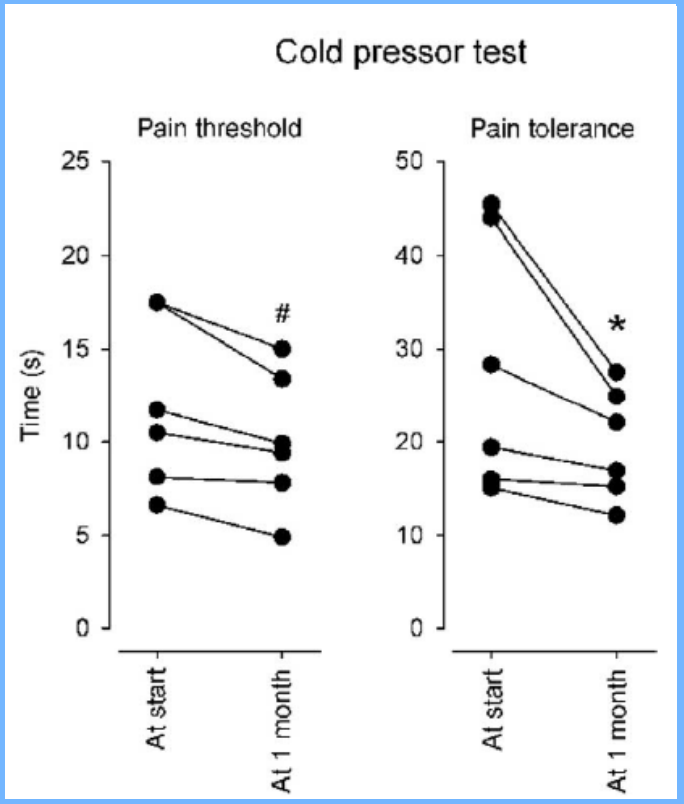


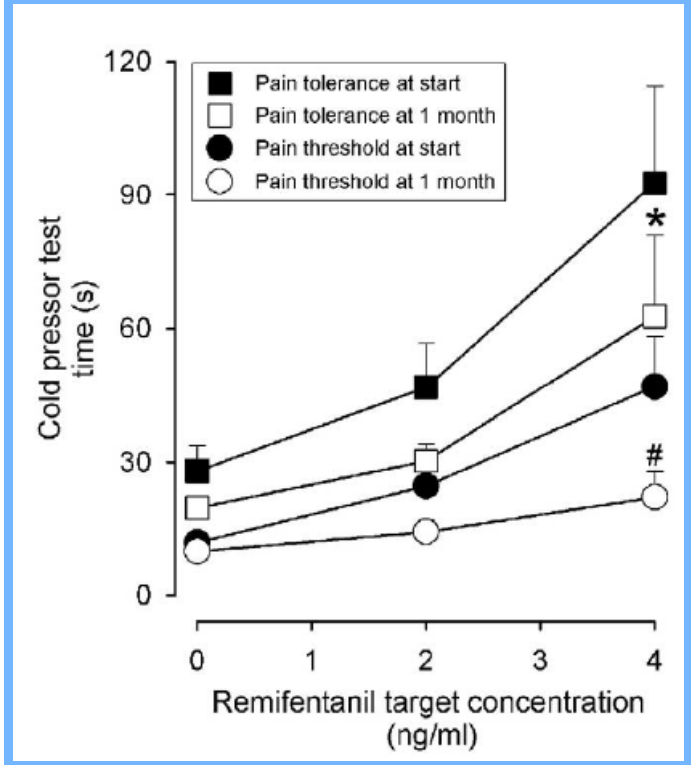
Rusy, LR, et al, In Press Anesthesia and Analgeisa 2010

Perioperative Management of Chronic Pain Patient

- Is the patient predisposed to increased postoperative pain?

Hyperalgesia in Chronic Pain Patients





- Patients on chronic opioids develop hyperalgesia to painful stimulation
- Patients on chronic opioids develop tolerance to opioid therapy for increased

Larry F. Chu,* David J. Clark,*,† and Martin S. Angst*

The Journal of Pain, Vol 7, No 1 (January), 2006: pp 43-48

Perioperative Management of Chronic Pain Patient

- How should we manage postoperative opioids in either the opioid tolerant or opioid-abusing patient?

Chronic Opioid Use

Chronic Pain Patient	Opioid-abusing Patient
Appropriate use of opioid	Out of control with opioids
Opioids improve quality of life	Opioids impair quality of life
Aware of side effects	Unconcerned of side effects
Follows treatment plan	Does not follow plan
Often has medications from prior prescriptions	Out of medications, loses prescriptions, drama

Mitra, S. and Sinatra, R., Anesthesiology 2004;101:212

Opioid Tolerant Patient

- Preoperative administration of baseline opioid
  - Oral or parenterally
  - Consider addition of adjuvant analgesics (NSAID's, gabapentin)
  - If told to not take AM medications, load with equivalent dose of drug
  - Continue implanted intrathecal pumps except consider reduction in baclofen
  - Avoid mixed agonist/antagonists; they may precipitate withdrawal

Opioid Tolerant Patient

- Intraoperative Management
  - Consider use of lipophilic opioids to titrate to intraoperative responsiveness
  - Doses will often be 30-100% greater than an opioid-naive patient
  - Dosing can be guided by baseline opioid use converted into a 1 hour requi
  - Remember oral to parenteral opioid conversion guidelines
    - Morphine 3:1
    - Hydromorphone 4-5:1
    - Oxycodone 1:1 with morphine IV
  - Consider reversal of neuromuscular blockade and then titrate opioid to res

Opioid Tolerant Patient

Postoperative Management

- Regional anesthesia is a great option
- For the extremely opioid tolerant patient, consider the use of neuraxial opioids
  - Conversions are roughly: 100:1 intrathecal; 10:1 epidural
  - Likely they will require supplemental oral or IV opioid to avoid withdrawal
  - Add local anesthetics to infusions
- PCA with basal equal to about 50%-100% of baseline hourly requirement; dose equal to 25-50% of baseline hourly requirement
- Early addition of methadone (Screen QTc) or another long-acting opioid
- Adjunctive use of NSAID's, ketamine, or neuromodulating drugs (gabapentin)

Anesthetic Considerations for the Chronic Pain Patient

- Patients with chronic pain challenge the pharmacologic knowledge-base of anesthesiologists
- Essentially no randomized controlled trials to guide evidence-based practice are available to aid in the perioperative management of these patients
- Nonetheless, integrating an understanding of the medications used to manage chronic pain with the postoperative analgesic needs of these patients leads to satisfactory perioperative care

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Perioperative Gabapentin

Morphine equivalents used in mg/kg/time

	Gabapentin	Placebo
Day 0 Total	**.044** (.017)	**.064** (.031)
Day 1 a.m.	.054 (.023)	.062 (.020)
Day 1 p.m.	.038 (.013)	.048 (.016)
Day 1 Total	**.046** (.016)	**.055** (.017)
Day 2 a.m.	.042 (.017)	.055 (.022)
Day 2 p.m.	.031 (.018)	.040 (.020)
Day 2 Total	**.036** (.016)	**.047** (.019)
Day 3 a.m.	.032 (.015)	.037 (.024)
Day 3 p.m.	.018 (.016)	.024 (.017)
Day 3 Total	.026 (.014)	.030 (.019)

Key: Bold results indicated significantly different results in mg/kg morphine equivalents consumed during day.