Clinical Implications of Opioid-Induced Hyperalgesia

Jianren Mao, MD, PhD

Richard J. Kitz Professor of Anesthesia Research
Harvard Medical School, Harvard University

Vice Chair for Research
Chief, Division of Pain Medicine
Director, MGH Center for Translational Pain Research
Department of Anesthesia, Critical Care and Pain Medicine
Massachusetts General Hospital

Disclosure of Conflict of Interest

None

ACHIEVEMENTS

New additions to various categories of pain medications

- Opioid analgesics
- NSAIDs; COX-2 inhibitors
- Ion channel (Ca^{++}, Na^{+}) blockers
- Antidepressants (TCA, SSRI, SNRI)
- Triptan drugs (5-HT1b, 1d receptor agonists) for migraine *
- Others (gabapentin, pregabalin) *

ACHIEVEMENTS

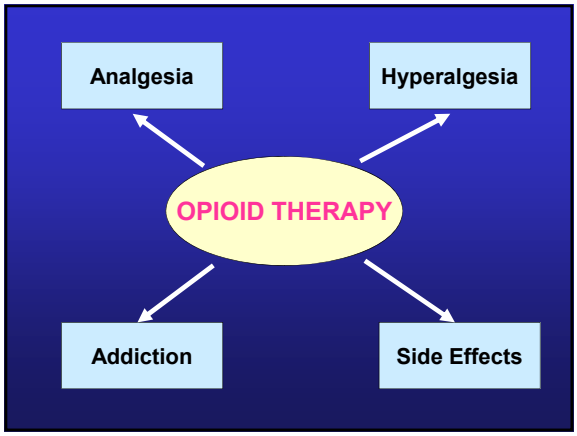
Innovative drug delivery methods and interventional procedures

- Topical agents (lidocaine, diclofenac, capsaicin)
- Intrathecal pump (opioid, local anesthetic, clonidine, baclofen)
- Neuro-modulation (spinal cord and deep brain stimulation)
- Transcutaneous electrical nerve stimulation (TENS)
- Others (RFL, sympathetic block, ESI, IDET, etc.)

ACHIEVEMENTS

Improvement in acute and postoperative pain management

- **PCA** (patient-controlled analgesia)
- **Regional nerve block**
- **Neuraxial block** (epidural, spinal)
- **Medication** (ketorolac – an intravenous NSAID)

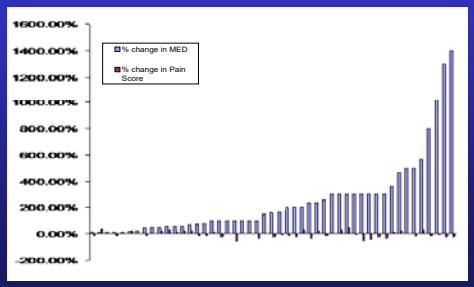


© 2019 Massachusetts Pain Initiative

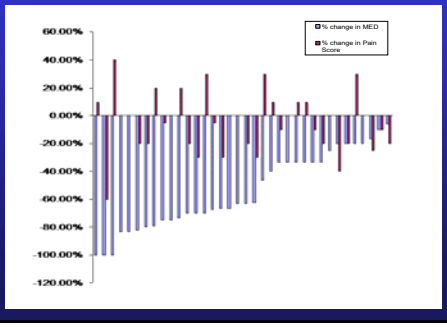
Does opioid dose adjustment change clinical pain score?

An analysis of a subgroup of over 100 chronic pain patients

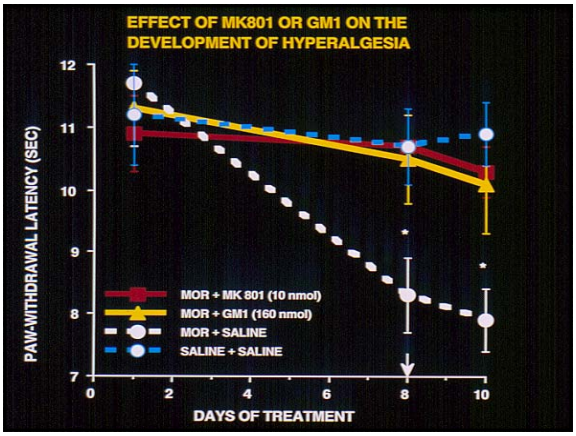
Opioid Dose Increase and Pain Score Change

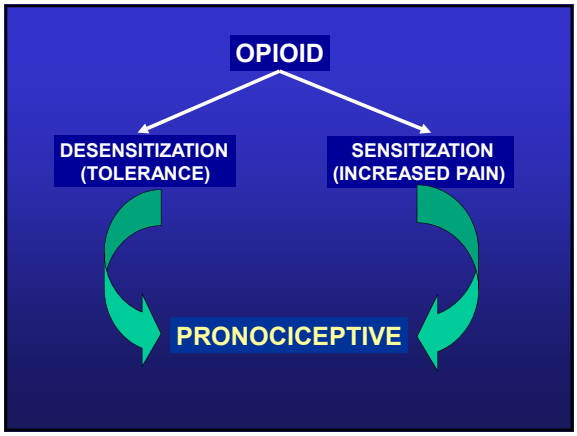


Opioid Dose Decrease and Pain Score



Opioid-Induced Hyperalgesia

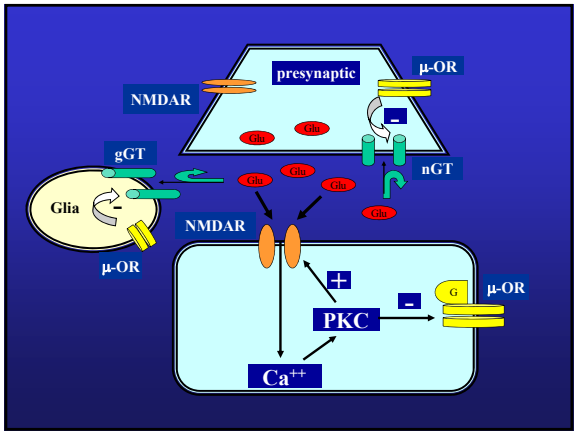




© 2019 Massachusetts Pain Initiative

NEURAL & MOLECULAR MECHANISMS

- Dynorphin
- Descending faciliation
- Alpha-2 Adrenergic receptor
- Glutamatergic system

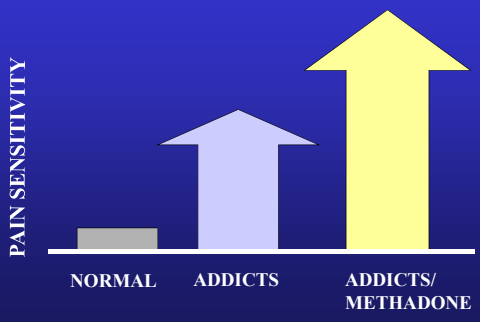


REPEATED OPIOID EXPOSURE

↓

A PATHOLOGICAL PAIN STATE

DATA FROM SUBJECTS WITH OPIOID ADDICTION

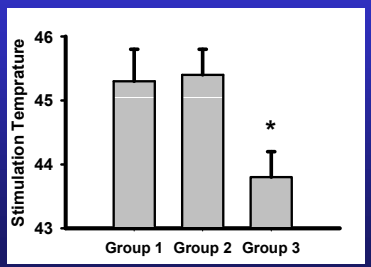


Martin & Inglis, 1965; Ho & Dole, 1979; Compton et al., 2001

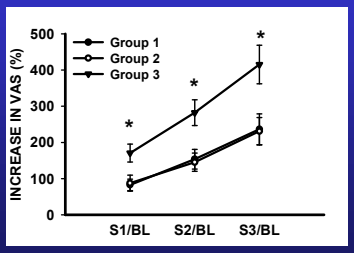
DECREASED ANALGESIC EFFICACY

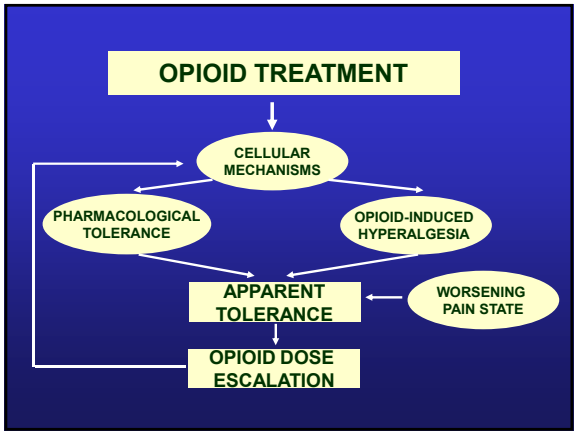
Cooper et al., 1997; Vinik & Igor, 1998; Guignard et al., 2000

Altered Heat Pain Threshold



Exacerbated Temporal Summation of Second Pain (Windup)

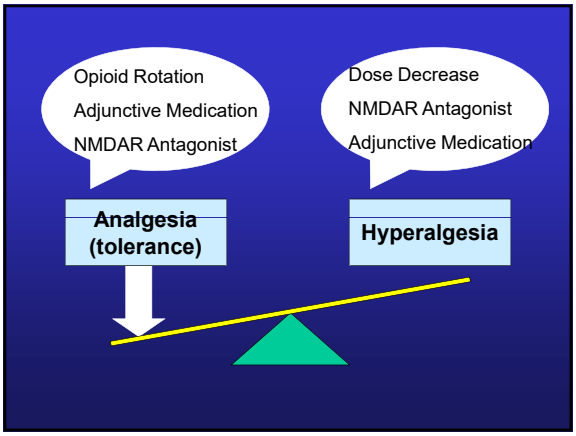




	OIH	Opioid tolerance
Exacerbated temporal summation of second pain	Yes	No
Decreased pain threshold	Yes	No
Decreased pain tolerance	Yes	No
Opioid dose (the higher, the more likely)	Yes	Yes
Duration of opioid therapy (the longer, the more likely)	Yes	Yes
Dose escalation	Limited improvement in clinical pain	Improvement in pain relief
Dose reduction	Improved opioid analgesia	Reduced opioid analgesia
Pain quality	Spontaneous, burning, diffuse pain similar to neuropathic pain	No change from pre-existing pain
Pain location	may ↑ dermatome distribution of the pre-existing pain	No change (from pre-existing pain)
Pain intensity	Similar to or greater than pre-existed pain	Similar to preexisted pain condition

Category I
- *Low dose*
- *Initial titration phase*

Category II
- *High dose; Long-term use*
- *Little change after dose titration*
- *Change in pain pattern*
- *Buprenorphine; methadone*



RELEVANCE: rat ≠ human

No complaint (affect, emotion)
No secondary gain
No comorbidity
No addiction
No legal issues
No illicit drug abuse
No socioeconomic challenge

© 2019 Massachusetts Pain Initiative

FUTURE DIRECTION

Animal models and assessment tools

We must consider pain-related comorbidities in animal models (e.g., depression, anxiety, drug addiction)!

Explore and validate new assessment tools (e.g., conditioned place preference; concurrent assessment of nociceptive and comorbid behaviors)

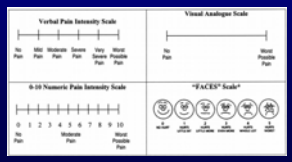
PAIN ASSESSMENT TOOL

Bench

Evoked response

Clinical

Pain rating
Pain questionnaires
Quantitative sensory testing



WHAT DOES PAIN SCORE TELL US?

VAS: 10/10

VAS: ??

ACKNOWLEDGEMENT

NIH Grants

R01 DA022576; P20 DA22576; R01 DA036564

MGH Center for Translational Pain Research

Lucy Chen, Shihab Ahmed, Yi Zhang, Charlen Malarick, Lindsey Seefeld, Mary Houghton, Christy Santana, Kristin Hilaire, Backil Sung, Grewo Lim, Shuxing Wang, Qing Zeng, Liling Yang, Yang Chang, Gabriel Rusanescu, Hyagine Kim, Yinghong Tian, Wei Zhang, Song Li, Jin Xu, Yonghui Tan, Masashi Ueda, Shuzhuo Zhang, Zerong You, Matthew McBride, Michael McCabe, Katherine Pokrass, Trang Vo, Abigail Sara Cohen, Cynthia Retamozo

© 2019 Massachusetts Pain Initiative