Chronic Pain
And Its Treatments

Yong X. Wang, MD & PhD

King’s Lab
Shanghai Jiao Tong University School of Pharmacy

yxwang@sjtu.edu.cn
http://kinglab.sjtu.edu.cn
Pain

• An unpleasant sensory and emotional experience associated with actual or potential tissue damage
• Subject’s personal feeling and can only be described by the patient, often but not always accompanying a series of signs and symptoms
• The fifth vital sign
Pain Perception

• Pain appreciation in peripheral tissue following activation of specialized pain sensors (nociceptors);
• Transmission of pain information from the periphery to the dorsal horn of the spinal cord where it is inhibited or amplified by a combination of local (spinal) circuits and descending tracts from higher brain centers;
• Onward passage of pain information to higher brain centers from which any appropriate action can be initiated;
• Efferent activities, particularly in animal pain studies.
Peripheral Nerve to Sensory Cortex via Spinal Cord (3 Levels for Pain Perception)

- Nociceptor
- Dorsal horn
- Sensory cortex

- Transduction
- Transmission
- Modulation
- Perception
- Interpretation
- Behavior
Peripheral Nerve to Sensory Cortex via Spinal Cord (3 Levels for Pain Perception)
Nociceptors

- Found in all tissues of the body except nervous tissue
- Convert noxious information into electrical information
- Are either chemical, thermal or mechanical in nature
- May have dual function as in mechanico-thermal nociceptors
Nociceptors and Pain Transmitters

Nociceptors
• Heat: TRPV1, P2X3, TRPV4,
• Cold: TRPM4, TRPA1
• H⁺: ASIC1, ASIC2, ASIC3
• Mediators: TRPV1, TRPA1, P2X3, P2X4, P2X7, 5-HT3, Nav1.8, Nav1.9, KCNQ, CaCCs

Pain Transmitters
• Substance P
• Glutamate
• CGRP
• Somatostatin
Capsaicin

• Indications
  – Postherpetic Neuralgia

• Mechanism
  – Derived from Jalepeno peppers
  – Activates TRPV1 receptors and depletes substance P from pain fibers
  – Requires frequent and repeat applications for effect; inconsistent use not effective

• Dose
  – Apply capsaicin cream to affected area 3-5 times daily

• Adverse effects
  – Burning sensation on initial application; increased pain for up to first week of application
Nociceptive Chemical Stimuli

**Activates PAN:**
(AP + Secondary Hyperalgesia)

- $K^+$
- $H^+$
- Serotonin
- Bradykinin
- Histamine

**Sensitizes PAN:**
(Allodynia, Primary Hyperalgesia)

- Leukotrienes
- Prostaglandins
- Substance P
# Types of Neuronal Axons

<table>
<thead>
<tr>
<th>Fiber Type</th>
<th>Relative Size</th>
<th>Myelinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aα</td>
<td>Large</td>
<td>Yes</td>
</tr>
<tr>
<td>Aβ</td>
<td>Large</td>
<td>Yes</td>
</tr>
<tr>
<td>Aδ</td>
<td>Small</td>
<td>Yes</td>
</tr>
<tr>
<td>C</td>
<td>Smallest</td>
<td>No</td>
</tr>
</tbody>
</table>
Peripheral Nerves: Types of Fibers

- Aα fibers
- Aδ fibers
- C fibers

myelin

spinal cord

peripheral nerve
Figure 6  The top cartoon shows what happens when you electrically stimulate a nerve fiber and record from upstream. There is a first quick “blip” and a second later “hill.” If you block a A delta fiber then all you get is the hill. If you block the C fiber, all you get is the quick blip.
Inhibition of Transmission: Membrane Stabilizing Drugs

myelin

$A_\delta$

nodes of Ranvier

Lidocaine

C

$K^+$

$Na^+$

$K^+$

$Na^+$

$K^+$

$Na^+$

$K^+$

$Na^+$

$K^+$

$Na^+$

$K^+$

$Na^+$

$K^+$

$Na^+$

$K^+$

$Na^+$

$K^+$

$Na^+$

$K^+$

$Na^+$

$K^+$

$Na^+$

$K^+$

$Na^+$

$K^+$

$Na^+$
Lidocaine

- **Action**: Na\(^+\) channel block
- **Indication**: peripheral neuropathic pain? others
  - Useful IV or topical
  - No reliable oral equivalent
- **Side effects**: similar rates to placebo for sedation, N/V, pruritis etc
  - CNS toxicity at plasma levels > 5 μg/mL
- **Dose**: IV 1-2 mg/kg/hr (??duration)
  - Patches available in USA and other countries
Dorsal Horn Neurons

- Projection cell
- High threshold (Aδ & C)
- Low threshold (Aα & Aβ)
- Primary afferents
- Interneurons

II
II₀
II₁
Dorsal Horn Receptors

Receptors on Post Synaptic Neurons

- PAN
  - 5-HT$_2$
- NK-1
- SP
- Glu
- K
- GABA$_B$
- 5-HT$_3$
- $\alpha_2$
- mu/delta

Excitatory:
- AMPA
- NMDA
- mu
- $\alpha_2$
- mu/delta
- NK-1
- 5-HT$_{1B}$

Inhibitory:
- GABA$_A$
- delta
- GABA$_A$
- Adn
- Adn
- GABA$_B$
Facilitation in Dorsal Horn

• Spinal cord level
  – A-delta and C fiber input
  – Substance P: NK-1 receptors
  – Non-NMDA receptors: AMPA and GABA?
  – NMDA Receptors: (N-methyl-D-aspartate) primed by previous input neural plasticity
Inhibition in Dorsal Horn

- Spinal cord level
  - GABA receptors: Baclofen
  - Glycine receptors: Gelsemine
  - Calcitonin receptors: Calcitonin
  - Somatostatin receptors: Octreotide
  - Alpha2 receptors: Clonidine
Sensory Cortex, and Influences of Emotion, Sleep and Memory on Pain

“一朝被蛇咬, 十年怕井绳”
Nociceptive Pain vs. Pathological Pain

Nociceptive pain – “Good” pain

Pathological pain – Bad pain
Nociceptive Pain

• Recent onset and limited duration; an identifiable cause relating to injury or disease, e.g., injury, post-operative pain. Normal manifestation of everyday life and serves a vital defense function - alarm system; e.g., congenital painless

• Not very difficult to treat
Etiology of Nociceptive Pain

Activation of primary afferent nociceptors by mechanical, thermal, chemical stimuli, or even infection

Only 20% of the body’s nociceptors are activated, but in response to tissue injury and inflammation, up to 100% of the body’s nociceptors may be activated.
Peripheral Transduction: Facilitation & Inhibition

<table>
<thead>
<tr>
<th>Facilitate transduction: (peripheral soup ingredients)</th>
<th>Inhibit transduction: (eliminate soup ingredients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandins</td>
<td>NSAIDs, Steroids</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>NSAIDs, Steroids</td>
</tr>
<tr>
<td>Histamine</td>
<td>Antihistamines</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Capsaicin</td>
</tr>
<tr>
<td>Substance P (injured nerves)</td>
<td>Anxiolytics &amp; Non-pharmacologic therapies</td>
</tr>
</tbody>
</table>

**NSAIDs:** Indomethacin, Ibuprofen, Diclofenac, Naproxen, Celecoxib
Peripheral Transduction: Nociceptive Chemical Stimuli

- Phospholipids released during trauma
- Arachidonic cascade
- Leukotrienes
- Cox2, Prostaglandins
- Ketoprofen
- ASA/NSAIDS
- Celebrex, Vioxx
- Thromboxane A2 platelet aggregation
- Steroids

Pain receptor
Neuropathic Pain

- Persists for long periods, usually beyond the time of tissue healing and for which the cause may not necessarily be easily identifiable
- Difficult to treat

Symptoms

Allodynia

Hyperalgesia

Spontaneous Pain

Pain emotion
Symptoms of Neuropathic Pain

Electric Hitting

Tearing

Electric Tingling

Burning

“在人类的历史长河中，疼痛始终伴随着岁月，有时比死亡更令人恐怖，是人类最恐怖最难忍受的痛苦之一”
Etiology of Neuropathic Pain

Peripheral or central nervous system tissue damage (ectopic and persistent discharge) or from altered processing of pain in the CNS – Central Sensitization
Pathological and Clinical Classification

Neuropathic Pain
- Postherpetic neuralgia
- Diabetic neuropathy
- Trigeminal neuralgia
- Sciatica
- Stroke neuropathy

Mixed Pain
- Low back pain
- Cancer pain

Nociceptive Pain
- Infection
- Bone fracture
- Acute arthritis
- Postoperation
- Exercise and sports

Chronic Pain (Pathological Pain)

Acute Pain (Physiological Pain)
Chronic Pain Incidence and Types

- Long than 1 month or > 3 or 6 months), or longer than tissue recovery; or refractory during years
- 20%? Population, cancer patients: 70-90%, AIDS: 50%
- Older, higher pain population
- 10% retractable pain
- Chronic pain is a disease

- Neuropathy (trigeminal neuralgia and sciatica)
- Cancer pain (chemotherapic pain)
- Rheumatoid arthritis
- Diabetic neuropathy
- Low back pain
- Migraine
- Gout
- Tooth ache
- Visceral pain
疼痛治疗：陈旧理念PK现代理念

- 术后疼痛有助于机体恢复？
- 疼痛，能忍就忍着，人生来就是受苦的？
- 我看你根本就不像痛，一点症状都没有？
- 疼痛只是疾病的症状，只要疾病治好了，疼痛就会消失？
- 镇痛药用多了以后会没药用？
- 疼痛是无益的
- 人生苦短，应尽量的享受生活，何必无谓的忍受痛苦
- 疼痛是病人说了算
- 免于疼痛是病人的基本人权！
- 疼痛应该及时控制，多开疼痛科，镇痛药要及时用
WHO Analgesic Ladder for Cancer Pain Patients (the Forth Ladder?)

- Mild to moderate pain lasting 3–4 hours
- Start with low doses of nonopioid drugs
- Intermediate pain or pain not well controlled with nonopioid
- Combine nonopioid with a low-dose opioid
- Severe pain
- Add a higher dose opioid to the nonopioid, or use a drug that potentiates its analgesic effect like an antihistamine
Mechanisms of Neuropathic Pain: NMDA Receptor-Mediated Sensitization, Disinhibition, and Glial Activation
Target Molecules for Chronic Pain

TCAs/SNRI: 
- Venlafaxine
- Fluoxetine

NMDA Receptor Antagonists:
- Ketamine

Opioids:
- Morphine
- Oxycodone
- Fentanyl

Corticosteroids:
- Prednisone

Anticonvulsants:
- Gabapentin
- Pregabalin

Topical Analgesics:
- Local anesthetics
- NSAIDs

Anti-inflammatory Drugs:
- Nonsteroidal anti-inflammatory drugs (NSAIDs)

Sympatholytics:
- Amodine

Topical Analgesics:
- Lidocaine

Muscle Relaxants:
- Carisoprodol

Antidepressants:
- Selective serotonin reuptake inhibitors (SSRIs)
- Tricyclic antidepressants (TCAs)

Endogenous Opioids:
- Enkephalins
- Beta-endorphins

Anticonvulsants:
- Valproic acid
- Gabapentin

Corticosteroids:
- Prednisone

Endogenous Opioids:
- Enkephalins
- Beta-endorphins

Antidepressants:
- Selective serotonin reuptake inhibitors (SSRIs)
- Tricyclic antidepressants (TCAs)
Dorsal Horn NMDA Receptors and Central Sensitization

- Spread diffusely over dorsal horn
- Facilitate pain transmission
- Activation threshold unchanged for high threshold nociceptive & WDR nociceptive projection cells
- Central (secondary) hyperalgesia
- Ketamine blocks NMDA receptor

- Ionotropic Glutamate receptor
- Excessive activation leads to neuronal cell death
- Knockdown of NR1 will protect cells against cell death
Ketamine

- **Action**: NMDA receptor antagonist
  - ‘anti-hyperalgesic', 'anti-allodynic' and 'tolerance-protective' agent
- **Indication**: Protective analgesia, NP treatment, opioid-tolerant patients
- **Side effects**: Dysphoria, nightmares, “psychedelic” effects
- **Dose**: Low doses usually well tolerated
  - Intra-op: 0.5mg/kg bolus then 0.25-0.5 mg/kg/hr (beware prolonged recovery)
  - Post-op: 0.1-0.2 mg/kg/hr (?duration)
Morphine

- Mainly activates \( \mu \)-opioid receptors in the descending inhibitory system and produces efficient analgesia
- Gold-standard analgesic
- Number one in pain market but not in China
Morphine Usage Issues in China

• 17世纪英国医生、临床医学奠基人Thomas Sydenham说: “我忍不住要大声歌颂伟大的上帝，这个万物制造者给人类痛苦带来了舒适的鸦片，无论从控制疾病的数量，还是从消除疾病的效率，没有一种药物比鸦片更有价值”

• God produces morphine

• 1.3 mg/per person in China but 17.8 mg in Developed countries

• Overdose deaths have quadrupled since 1999

• New class: MOR-NRI: tapentadol, dezocine, and pentazocine?

Vivek Murthy Sent A Unprecedented Letter About Opioids To Every Doctor In America (8/25/2016)
Annual Sales of Dezocine and Morphine and Their Opioid Analgesics Shares in China
Endogenous Morphine-Like Substances

- Endogenous morphine-like substances include enkephalins, β-endorphin and dynorphin A
- β-Endorphin contents are reduced in pain patients
- β-Endorphin release is involved in placebo-, acupuncture-, SPA-, exercise-induced analgesia
- β-Endorphin produces analgesia and analgesic tolerance
- Dynorphin A produces analgesia without induction of analgesic tolerance
Lamiophlomis Rotata (独一味), A Widely-Prescribed Oral Tibetan Herbal Analgesic

• Widely used for wound and pain for thousand years;
• Embodied in Chinese Pharmacopoeia for the treatment of pain and hemostasis;
• Meta-Analysis shows efficacy in analgesia in mild/medium chronic pain including cancer pain;
• Annul Sales of US$30 million.
Oral *L. Rotata* Aqueous Extract Specifically Inhibits Pain Hypersensitivity

Zhu et al., Anesthesiology, 2014
Ingredients of *L. Rotata*

- **Flavonoids** (黄酮)
  - Rutin (芦丁), luteolin, apigenin, quercetin (木犀草素)
- **Iridoid glucosides** (环烯醚萜苷)
  - Shanzhisle methyl ester (SM) (山栀子苷甲酯), 8-O-acetyl-SM (乙酰山栀子苷甲酯),
  - Geniposide (京尼平苷), Loganin (马钱子苷), penstemoside Lamiophlomiol A and B,
- **Quality control ingredients listed in the China Pharmacopia**
  - SM and 8-O-acetyl-SM (1-3%)
Chemical Structures of Geniposide, SM, 8-O-Acetyl-SM and Other Iridoids

- Geniposide
- Geniposidic acid
- Genipin
- Methylgenipin
- 1,10-Anhydrogenipin
- Loganin
- Catalpol
- Shanzhiside methylester
- 8-O-Acetylshanzhiside methylester
Oral *L. Rotata*-Derived Total Iridoid Glycosides (but not Flavonoids) Inhibit Formalin Hyperalgesia

Zhu et al., Anesthesiology, 2014
Spinal Cord Is A Primary Site for *L.* Rotata and SM to Produce Antinociception

Zhu et al Anesthesiology 2014
Fan et al Neuropharmacology 2016
SM Does not Induce Analgesic Tolerance or Morphine Analgesic Tolerance

Fan et al Neuropharmacology 2016
Newly Discovered Spinal Microglial GLP-1R/β-Endorphin Pathway

Gong et al J Neurosci 2014
Fan et al Neuropharmacology 2016
SM Is An Orthosteric, Reversible and Fully Intrinsic Agonist of GLP-1Rs

Zhu et al., Anesthesiology, 2014
Exendin(9-39) and siRNA Block Antinociceptive Effects of *L. Rotata* and SM

Zhu et al., Anesthesiology, 2014
SM Secrets Minocycline-Sensitive β-Endorphin Release from Spinal Microglia

Fan et al Neuropharmacology 2016
SM Produces Antinociception by Stimulating Spinal Microglial β-Endorphin Release

Fan et al Neuropharmacology 2016
SM and Exenatide Specifically Activate Spinal p38 MAPK, but not ERK1/2 or JNK.
p38 MAPK Phosphorylation Inhibitor Blocks SM Antiallodynia in Neuropathy

B

Contralateral

Ipsilateral

Post Intrathecal Injection of SM (hrs)

Inhibitor
L. Rotata Activates Spinal GLP-1R/β-Endorphin Pathway to Produce Analgesia
Advances in Treatments for Neuropathic Pain

• Botulinum toxin: low back pain
• Lidocaine patch 5%: low back pain, osteoarthritis, diabetic and HIV-related neuropathy, with gabapentin
• CR oxycodone: diabetic neuropathy
• Gabapentin and pregabalin: HIV-related neuropathy, diabetic peripheral neuropathy, others
• Levetiracetam: neuropathic pain and migraine
• Oxcarbazepine: neuropathic pain; diabetic neuropathy
• Bupropion: neuropathic pain
• Transdermal fentanyl: low back pain
Peripheral Nerve Damage Induces Upgrade and Trafficking of Spinal and DRG $\alpha2\delta$ Subunit

### A.

<table>
<thead>
<tr>
<th></th>
<th>Dorsal S.C.</th>
<th>L5/6 DRG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sham</strong></td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td><strong>Ligated</strong></td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td><strong>Sham</strong> (+)</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

![Image of protein expression](image)

### B.

**α2 Protein Level (% contral. side)**

- **Sham**
- **Ligated**
- **Sham 56**

![Graph showing protein level](image)
Pregabalin Inhibits Upgrade and Trafficking of α2δ Subunit, and Transmitter Release
## Guidelines for Gabapentin and Pregabalin to Treat Neuropathic Pain

<table>
<thead>
<tr>
<th>Guidance</th>
<th>Year</th>
<th>Status</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK NICE</td>
<td>2010 年</td>
<td>First line</td>
<td>Central and peripheral neuropathy</td>
</tr>
<tr>
<td>USA ICSI</td>
<td>2008年</td>
<td>A Grade Recomm.</td>
<td>Postherpetic neuralgia, diabetic neuropathy</td>
</tr>
<tr>
<td>Canada CPS</td>
<td>2007年</td>
<td>First line</td>
<td>Chronic neuropathic pain</td>
</tr>
<tr>
<td>IASP</td>
<td>2010年</td>
<td>First line</td>
<td>Neuropathic pain</td>
</tr>
<tr>
<td>USA ASPE</td>
<td>2006年</td>
<td>First line</td>
<td>diabetic neuropathy</td>
</tr>
<tr>
<td>Europe EFNS</td>
<td>2010年</td>
<td>First line</td>
<td>Postherpetic neuralgia, Central and peripheral neuropathy</td>
</tr>
<tr>
<td>USA AAN</td>
<td>2004年</td>
<td>A Grade Recomm.</td>
<td>Postherpetic neuralgia</td>
</tr>
</tbody>
</table>
### World-Wide Uses of Gabapentin and Pregabalin for Neuropathic Pain

<table>
<thead>
<tr>
<th>适应症</th>
<th>被批准国家及地区</th>
</tr>
</thead>
<tbody>
<tr>
<td>癫痫部分发作的辅助治疗（12岁以上儿童、成人）</td>
<td>美国，欧洲，南美洲，中东，北非，香港，澳门，印度，马来西亚，新西兰，巴基斯坦，菲律宾，新加坡，台湾，泰国，越南，新西兰</td>
</tr>
<tr>
<td>焦虑症</td>
<td>哥伦比亚</td>
</tr>
<tr>
<td>纤维肌痛(FMS)</td>
<td>美国，加拿大，南美洲，中东，北非，香港，印度，韩国，马来西亚，菲律宾，新加坡，泰国</td>
</tr>
<tr>
<td>广泛性焦虑障碍(GAD)</td>
<td>欧洲，南美洲，中东，北非，香港，印尼，马来西亚，新加坡，泰国，越南</td>
</tr>
<tr>
<td>神经病理性疼痛(Nep)</td>
<td>欧洲，南美洲，中东，北非，南非，澳大利亚，香港，印度，印尼，韩国，澳门，马来西亚，新西兰，巴基斯坦，菲律宾，新加坡，泰国，越南</td>
</tr>
<tr>
<td>中枢NeP</td>
<td>欧洲，南美洲，中东，北非，泰国，香港，印尼，泰国</td>
</tr>
<tr>
<td>外周NeP</td>
<td>欧洲，南美</td>
</tr>
<tr>
<td>糖尿病周围神经痛(DPN)</td>
<td>美国，加拿大，南非，南美洲，</td>
</tr>
<tr>
<td>带状疱疹后神经痛(PHN)</td>
<td>美国，加拿大，南非，中国</td>
</tr>
</tbody>
</table>
Ziconotide (Prialt®)

A New Analgesic from the Venom of the Cone Snail (芋螺)

For treatment of severe, chronic pain
Cone Snail-Derived Ziconotide (Prialt®)

Olivera's boyhood fascination with cone snails led him to the discovery of a powerful painkiller.
Ziconotide Inhibits Synaptic Transmission at a Subset of Synapses

- Ziconotide blocks presynaptic N-type calcium channels
- The N-type calcium channel is one of several presynaptic calcium channel subtypes
- The distribution of N-channels determines ziconotide’s:
  - therapeutic utility
  - side effect profile
  - route of administration
N-Type Calcium Channels Are Widely Distributed in the Brain
N-Type Channels Localized in Outer Layers of Dorsal Horn

Ziconotide Binds to N-type VSCCs
• Preventing calcium entry into neurons
• Modulating membrane excitability
• Inhibiting neurotransmitter release
Ziconotidide Blocks Pain Signals Entering the Spinal Cord

N-type calcium channels are densely expressed in the spinal cord where pain-sensing nerves terminate.
Ziconotide Is Analgesic in Animals
Tolerance Develops to Morphine
Tolerance Does not Develop to Ziconotide
Morphine Is Not Effective in the SNL Model Ziconotide Is Maximally Effective

Rat sensory nerve ligation model
Ziconotide vs Morphine: Preclinical profile

- Highly efficacious in neuropathic pain models
- >1,000 times more potent
- No tolerance (self and cross)
- No addition
- No significant respiratory depression or cardiovascular effects (intraspinal administration)
- Intraspinal administration
- Supraspinal behavioral effects
Intraspinal Drug Delivery

- Direct to site of action
- Low systemic exposure
- Technically elegant
- Reliable
- Expensive
- Invasive
- Refractory patients only
The Ziconotide Patients

- Pain Intensity = 74
- Duration = 12 years
- 76% Neuropathic
- Medications = 11
- Multiple Operations
- 62% Depression
- Suicide Risk High

- 92% Can’t work
- 90% Can’t sleep
- 88% Can’t walk
- 59% Driving restrictions
- 55% Pain dominates life

Ziconotide was the last option for many patients
Pivotal Phase 3 Trials

- Randomized, double-blind, parallel comparison to placebo
- Chronic pain patient populations
  - Nonmalignant conditions or injuries: nonmalignant pain study; \( n = 256 \)
  - Cancer or AIDS: malignant pain study; \( n = 112 \)
- Long-term, open-label follow-up for responders; \( n = 155 \)
Primary Efficacy Measure of Analgesia

% change in VASPI from pre-infusion to end of initial dose titration

VASPI: Visual Analog Scale of Pain Intensity (0 to 100)
Results of Phase 3 Studies

* $p < 0.001$

![Graph showing VASPI % Improvement for Nonmalignant and Malignant conditions with Ziconotide and Placebo.](image-url)
Ziconotide Clinical Studies Summary

- Effective against a variety of pain types, including neuropathic pain syndromes
  - >1500 patients have received ziconotide
  - Two pivotal Phase 3 trials successfully completed
- Effective in patients unresponsive to any other systemic or intra-spinal analgesics
- Efficacy maintained for >12 months
  - No evidence of tolerance
- Safety issues thoroughly explored
  - Safely used with concommitant opiates
  - Narrow therapeutic ratio, but wide safety margin
Ziconotide: Adverse Events (Typically Dose-Related)

- Abnormal gait
- Dizziness
- Nystagmus
- Confusion
- Somnolence
- Fever
- Postural hypotension
- Urinary retention
- Nausea and vomiting
Update on Laura:

- Off all other drugs!
- Married!!
- Expecting!!!
Thank You for Your Attention!