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Opioids in chronic non cancer pain

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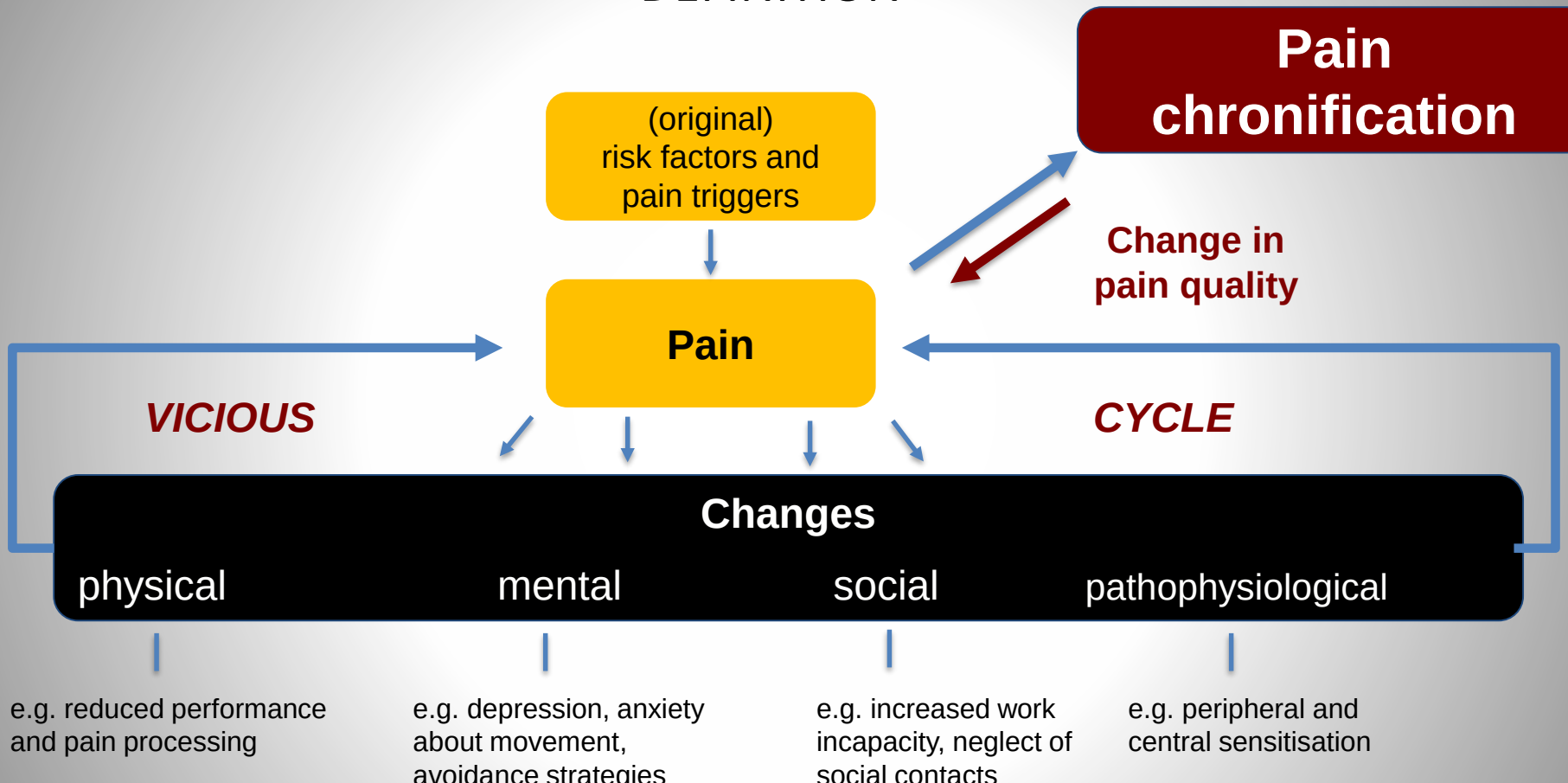
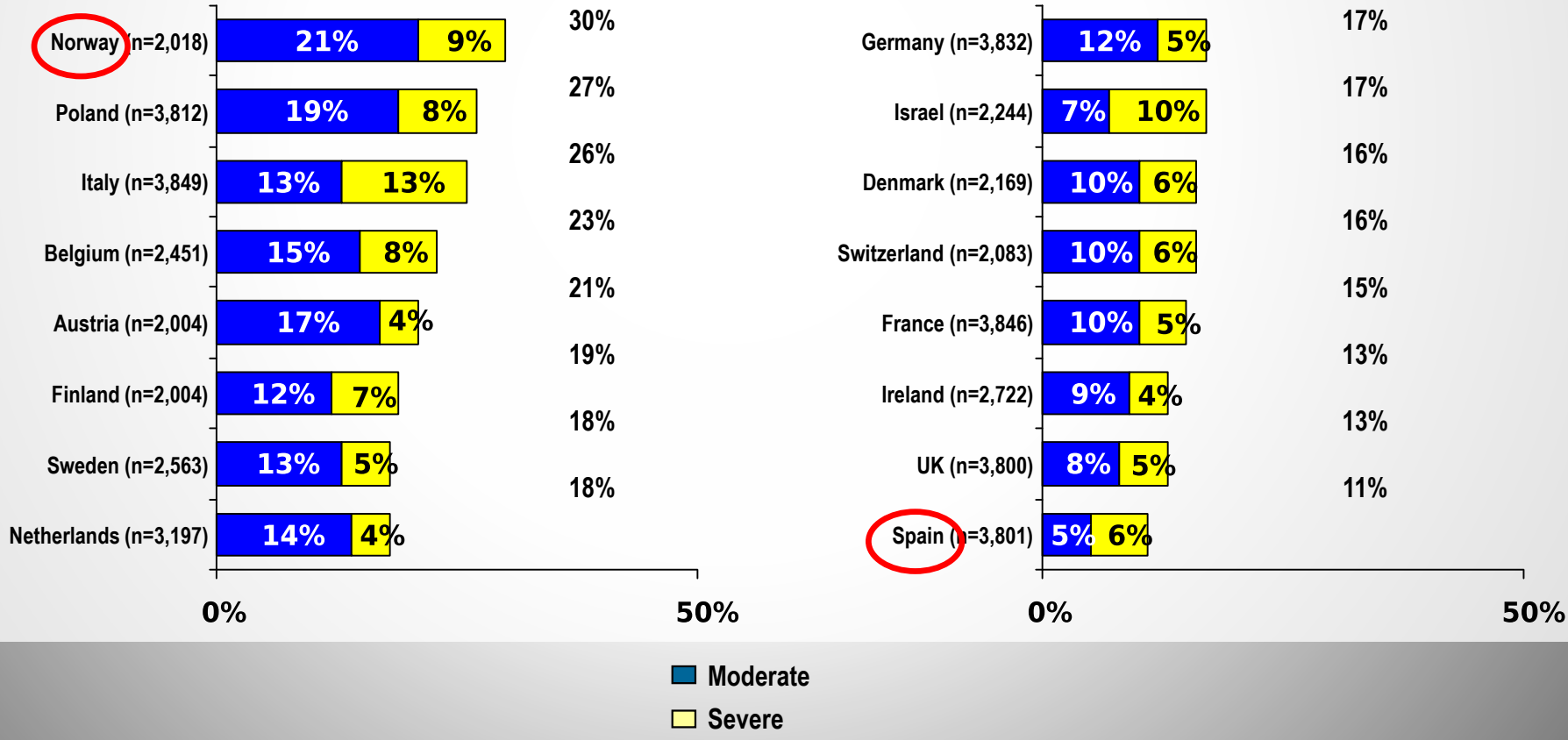
PAIN CHRONIFICATION DEFINITION



Prevalence of Chronic Pain by Country
– *Based on Complete Screener Data* –

Overall Prevalence = 19% (n=46,394)

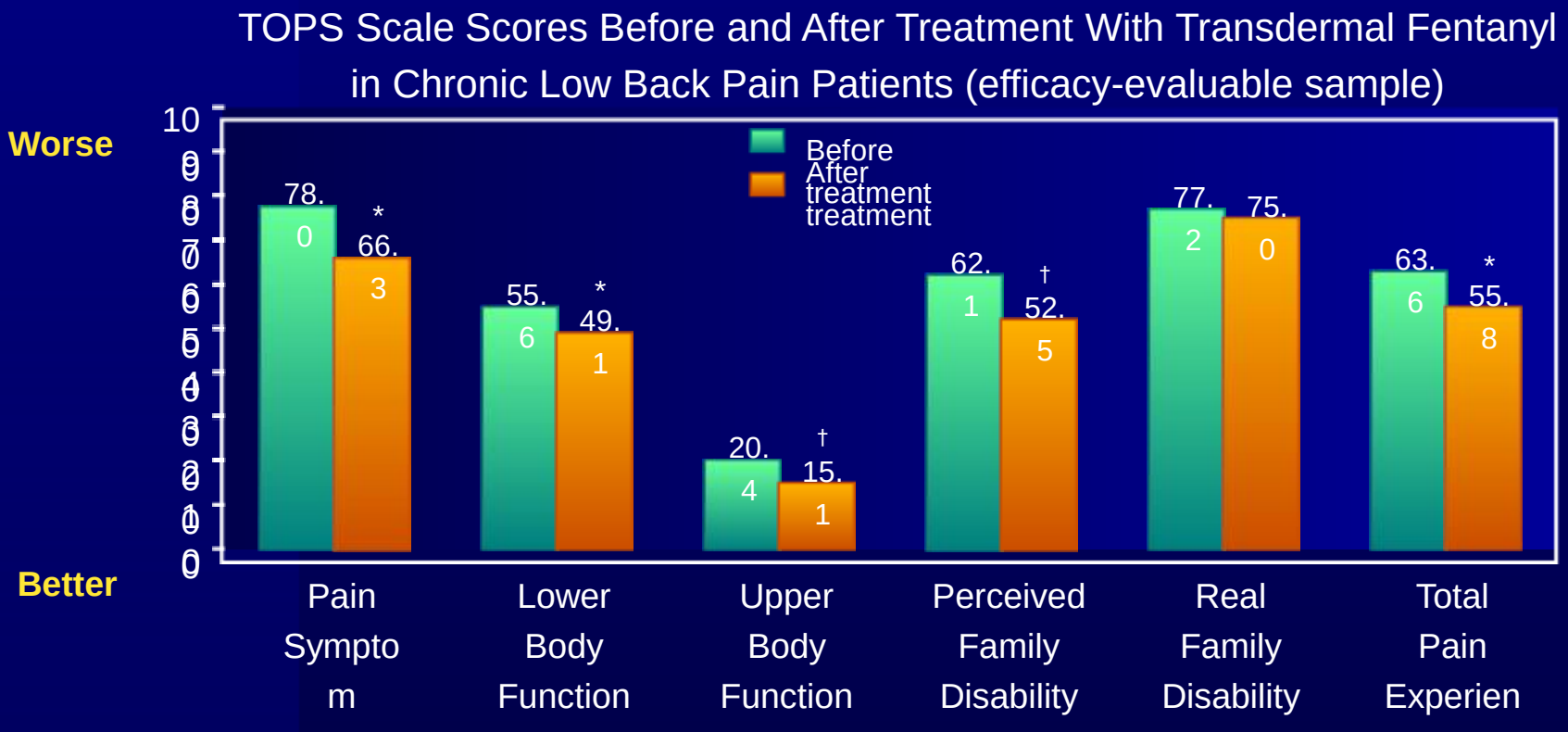
Moderate 13% Severe 6%



American College of Rheumatology 2012
Recommendations for the Use of
Nonpharmacologic and Pharmacologic Therapies
in Osteoarthritis of the Hand, Hip, and Knee

- Pharmacologic modalities conditionally recommended for the initial management of patients with knee OA included acetaminophen, oral and topical NSAIDs, tramadol, and intraarticular corticosteroid injections
- Intraarticular hyaluronate injections, duloxetine, and **opioids were conditionally recommended** in patients who had an inadequate response to initial therapy
- **Opioid analgesics were strongly recommended in patients who were either not willing to undergo or had contraindications for total joint arthroplasty after having failed medical therapy.**
- Recommendations for hip OA were similar to those for the management of knee OA.

Opioid Treatment Improved Health-Related Quality of Life: Fentanyl and Chronic Low Back Pain



*P<.001; †P<.01. TOPS=Treatment Outcomes in Pain Survey.

Reprinted with permission from Kosinski MR et al. *Curr Med Res Opin.* 2005;21:849-862.

Pharmacological management of chronic neuropathic pain - consensus statement and guidelines from the Canadian Pain Society.

- ***Recommendations for treatment are based on degree of evidence of analgesic efficacy, safety, ease of use and cost-effectiveness.***
- **First-line treatments ..... antidepressants (tricyclics) and anticonvulsants (gabapentin and pregabalin).**
- **Second-line treatments …….. serotonin noradrenaline reuptake inhibitors and topical lidocaine.**
- **Tramadol and controlled-release opioid analgesics are recommended as third-line treatments for moderate to severe pain.**
- **Fourth-line treatments include cannabinoids, methadone and anticonvulsants with lesser evidence of efficacy, such as lamotrigine, topiramate and valproic acid.**
- **Further studies are required to examine head-to-head comparisons among analgesics, combinations of analgesics, long-term outcomes, and treatment of pediatric and central NeP.**

Pain Res Manag. 2007 Spring;12(1):13-21

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Stamer U.M.

Genetics and variability in opioid response

Eur J Pain 2005; 9: 101-104

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Impatto del polimorfismo del cit P450 sulla terapia farmacologica

Isoenzima P450	Matobalized drugs	Side effects
CYP2C9	Warfarin Fenitoina NSAIDs Tolbutamide	bleeding atassia emorragy GI ipoglicemia
CYP2C19	inib pump Diazepam	sedation
CYP2D6	Antidepressivi triciclici Beta bloccanti Antiaritmici Aloperidolo Antag 5HT3 Codeine tramadol	Sedaztion Overdose Aritmia Parkinson Nausea, No analgesia Reduced analgesia

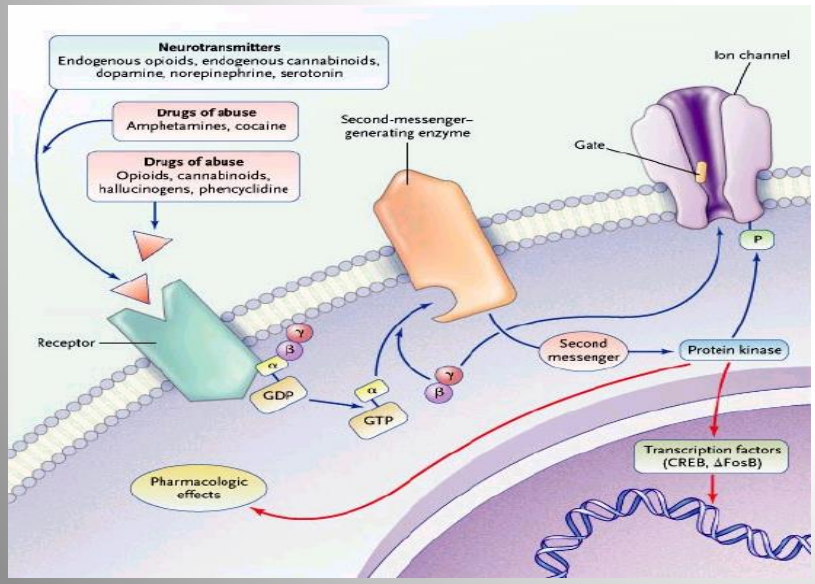
TOLLERANCE

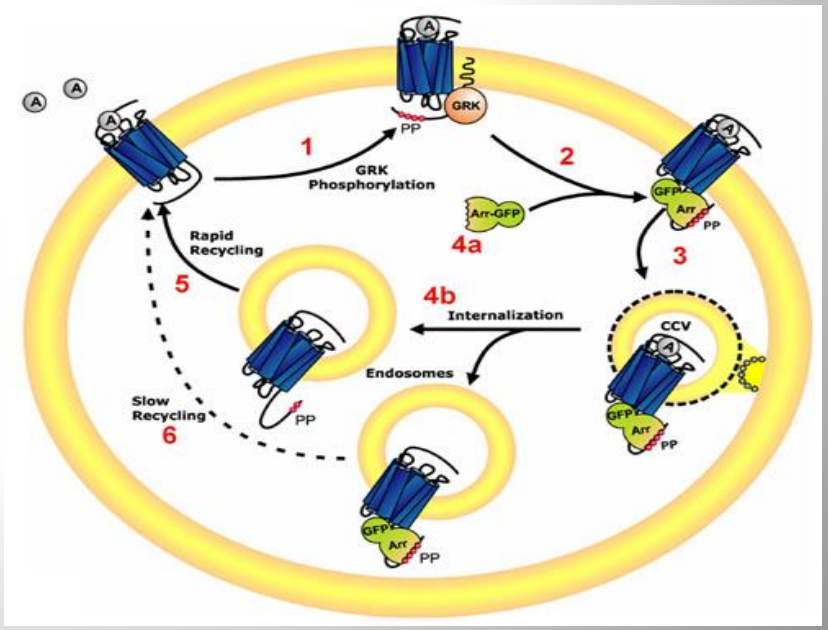
The Role of Opioid Receptor Internalization and β-Arrestins in the Development of Opioid Tolerance

Zhiyi Zuo, MD, PhD
Department of Anesthesiology, University of Virginia, Charlottesville, Virginia

Opioid tolerance, a phenomenon characterized by decreased analgesic effects obtained by the same dose of opioids after repeated use of the opioids, is a significant clinical problem. Traditional theory attributes receptor desensitization and internalization and post-receptor adaptation to the development of opioid tolerance. However, morphine, a commonly used opioid, induces tolerance but is not an effective drug to induce opioid receptor desensitization and internalization. Recent studies found that internalized opioid receptors can become competent receptors and recycle back to the cell surface membrane after dephosphorylation. Thus, receptor internalization may be a way to reduce opioid tolerance. Multiple studies have suggested a key role of β-arrestins in opioid receptor desensitization and internalization and opioid tolerance. Although β-arrestin 1 and β-arrestin 2 are important for these effects induced by opioids with high intrinsic efficacy such as etorphine and fentanyl, morphine tolerance may be mediated mainly via β-arrestin 2. Modification of opioid receptor internalization by affecting the interaction between opioid receptors and β-arrestins may be a therapeutic target for reducing opioid tolerance.

(Anesth Analg 2005;101:728–34)





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Opioid Rotation

- **Sequential trial of different opioids to obtain the most favorable balance between analgesia and adverse effects[1,2]**
- **Reasons for opioid rotation[3]**
  - Substantial variability in patient response
  - Inadequate analgesia
  - Intolerable adverse effects
  - Chronic sedation

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1. Fine PG. *J Pain Palliat Care Pharmacother.* 2004;18:75-79. 2. Bruera E, Kim HK. *JAMA.* 2003;290:2476-2479. 3. Fine PG, Portenoy RK. *A Clinical Guide to Opioid Analgesia.* Minneapolis: McGraw-Hill; 2004.

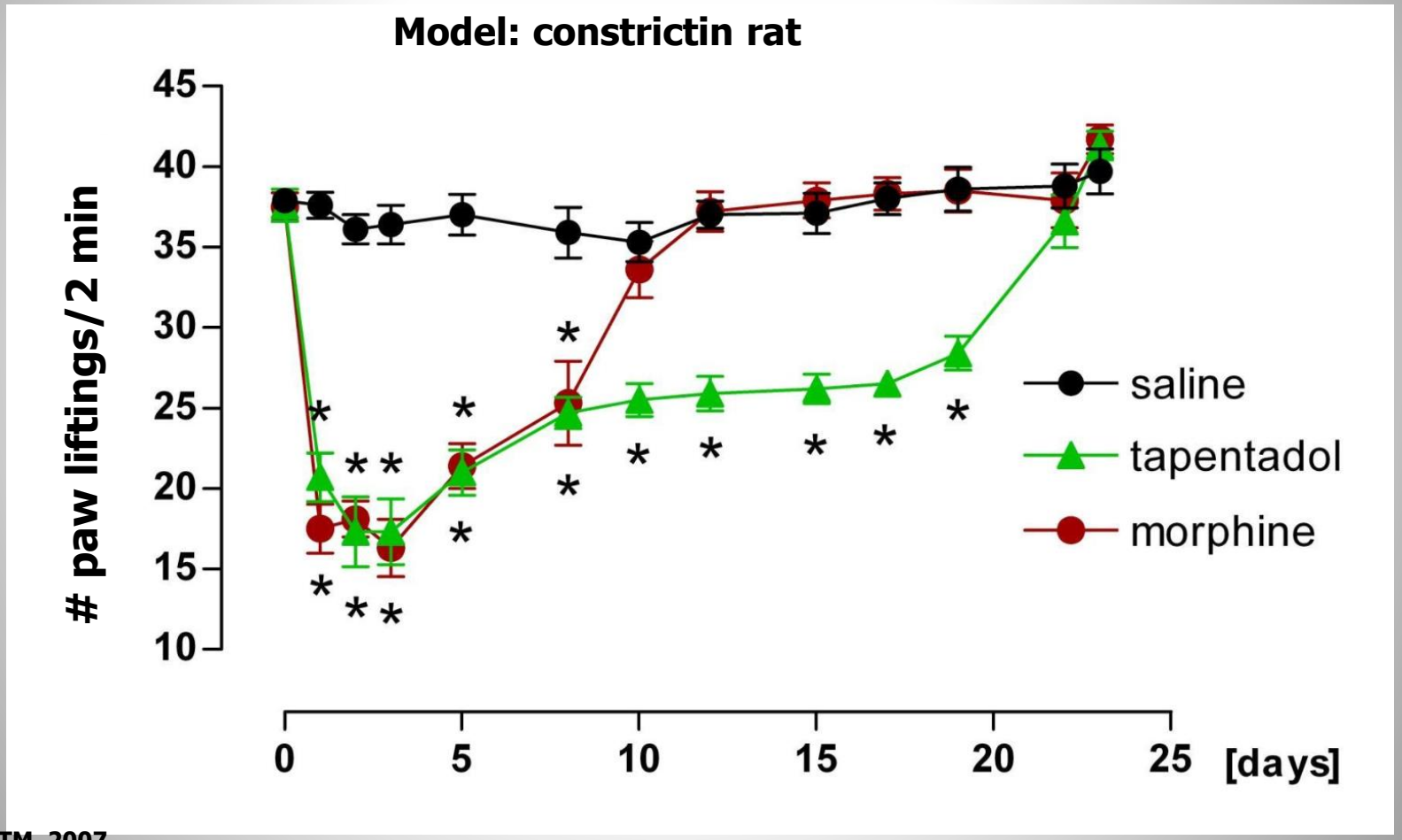
Br J Pharmacol. 2017 Apr 5. doi: 10.1111/bph.13809. [Epub ahead of print]

Targeting multiple opioid receptors - improved analgesics with reduced side effects?

…..Analgesic effects can also be mediated through other members of the opioid receptor family such as the κ-opioid receptor (κ receptor), δ-opioid receptor (δ receptor) and the nociceptin/orphanin FQ peptide receptor (NOP receptor).

Currently, a new generation of opioid analgesics is being developed that can simultaneously bind with high affinity to multiple opioid receptors. With this new action profile, it is hoped that additional analgesic effects and fewer side effects can be achieved.

Tapentadol: delayed development of tolerance in chronic pain compared to morphine



Tzschentke TM, 2007

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Mao J.

Opioid-induced abnormal pain sensivity: implications in clinical opioid therapy

Pain 2002, 100: 213-217

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- Hypersensitivity induced by opioid: increased opioid dose to obtain expected analgesia or inexplicable pain exacerbation after a period of effective opioid therapy.

- The increase in opioid dose is not always the adequate response to ineffective opioid therapy. Sometimes the opioid dosage reduction is more effective.

- This approach must be accompanied by the rotation of opioid and / or the association of non-opioid drugs.

- Evidence-based studies have suggested new strategies to prevent the development of drug tolerance and opioid-induced hypersensitivity such as the combined use of an opioid and an NMDA receptor antagonist

Opioids and bone pain

- Weak and strong opioids are essential in the treatment of severe and persistent pain caused by osteoporosis
- In inflamed tissues the interaction between opioids derived from leukocytes and opioid receptors can contribute to a potent and clinically relevant inhibition of pain
- Emerging problem:
  - high doses of opioids for chronic non-cancer pain can be associated with an increased risk of fracture confirmed by medical record review

J Gen Intern Med 25(4):310–5

Opioid Dependence, Tolerance, Pseudoaddiction, and Addiction

What are the differences?

- **Physical dependence:** Withdrawal syndrome would occur if the medication is discontinued abruptly, dose is reduced rapidly, or an antagonist is administered[1,2]
- **Tolerance:** A greater amount of medication is needed to maintain therapeutic effect, or loss of effect over time[2]
- **Pseudoaddiction:** Behavior suggestive of addiction caused by undertreatment of pain[2]; can be a major barrier to appropriate treatment of patients in pain
- **Addiction (psychologic dependence):** A biopsychosocial disorder characterized by continued compulsive use of a substance despite harm[2,3]

1. APS. *Guideline for the Management of Cancer Pain in Adults and Children.* Glenview, Ill: American Pain Society; 2005.
2. Savage SR et al. *APS Consensus Statement.* Glenview, Ill: American Pain Society; 2001. 3. Fishbain DA et al. *Clin J Pain.* 1992;8:77-85.

Postgrad Med. 2017 Jan;129(1):102-110.

Current and future development of extended-release, abuse-deterrent opioid formulations in the United States.

- **Prescription opioid misuse and abuse in the United States (US) is epidemic and is a major burden on health-care resources and costs to society.**
- The need to significantly reduce the risks of prescription opioid misuse and abuse must be balanced with the important needs of patients with chronic pain who may benefit from treatment with opioids.
- The use of abuse-deterrent formulations (ADFs) of prescription opioids is one approach that could reduce the risk of prescription opioid abuse and misuse while maintaining access to opioids

Pain Physician. 2017 Feb;20(2S):S3-S92.

Responsible, Safe, and Effective Prescription of Opioids for Chronic Non-Cancer Pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines.

- Establish treatment goals of opioid therapy with regard to pain relief and improvement in function. (Evidence: Level I-II; Strength of Recommendation: Moderate

- Consider up to 40 morphine milligram equivalent (MME) as low dose, 41 to 90 MME as a moderate dose, and greater than 91 MME as high dose. (Evidence: Level II; Strength of Recommendation: Moderate)

- Monitor for side effects including constipation and manage them appropriately, including discontinuation of opioids when indicated. (Evidence: Level I; Strength of Recommendation: Strong)iv.
- . May continue with monitoring with continued medical necessity, with appropriate outcomes. (Evidence: Level I-II; Strength of Recommendation: Moderate)
- Discontinue opioid therapy for lack of response, adverse consequences, and abuse with rehabilitation.

Pain Physician. 2017 Feb;20(2S):S3-S92.

Responsible, Safe, and Effective Prescription of Opioids for Chronic Non-Cancer Pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines.

CONCLUSIONS: ……., based on randomized controlled trials (RCTs) to improve pain and function in chronic non-cancer pain on a long-term basis.

Consequently, chronic opioid therapy should be provided only to patients with proven medical necessity and stability with improvement in pain and function, independently or in conjunction with other modalities of treatments in low doses with appropriate adherence monitoring and understanding of adverse events.

……..

Disclaimer: The guidelines are based on the best available evidence and do not constitute inflexible treatment recommendations. Due to the changing body of evidence, this document is not intended to be a "standard of care."

Guidance on opioids prescribing for the management of persistent non-cancer pain in older adults.

Formulating an effective treatment plan for older adults with persistent pain requires a clear understanding of comorbidities and psycho-social situation. However, common opioid-related harms can be minimized with an individualized approach to opioid prescribing tailored to patients' health status and risk factors.

Kress H.G.

Opioid medication and driving ability

Eur J Pain 2005; 9: 141-144

- The decision to drive during opioid treatment is always a personal decision
- The patient must be fully informed, cooperative and compliant and must be in good physical and mental general conditions
- Patients should be reminded that the responsibility of their physical state is to be taken momentarily by themselves
- Continuous therapy monitoring is the duty of the physician
- A written document is required

European Review for Medical and Pharmacological Sciences 2015; 19: 4898-4905

Opioid risk addiction in the management of chronic pain in primary care: the addition risk questionnaire

...re for each question and an overall score to identify patients at risk. This questionnaire, until its validation, shows a list of information that the doctor can obtain from the medical history of the patient.

N.	Questionnaire	Yes	No
1	I'm / I smoked in my life for more than six months continuously		
2	I take an alcoholic drink every day before meals or a digestive after meals		
3	I use / I have used drugs to treat anxiety and depression		
4	My parents, brothers or sisters have had the need to take drugs for the treatment of anxiety and depression		
5	I use / have used drugs in my life for more than six months continuously		
6	In my family there were problems with drugs or alcohol		

		Totally agree	Quite agree	Neither agree nor disagree	Quite disagree	Strongly disagree
7	I spend more time than I should every day in front of the PC, smartphone or console not for work					
8	I always run the risk of taking penalties / fines in my life					
9	Because of my behavior I changed school several times					
10	I often try the luck					
11	The drugs can not help me heal my pain					
12	I've always been considered a troubled student by teachers					
13	I can always control my anger					
14	Everybody hates me					
15	I often like to look for exciting experiences					
16	I always want to exceed the limit					
17	When I wake up, I immediately desire to smoke					
18	I have been criticized for the way I drink					
19	I have a satisfying sex life					
20	After all sexual relations, although satisfactory, I feel the need to have others in a short time					
21	I have a lot of trust into myself					
22	During this time I have problems at work					
23	During this time I have problems in the family					
24	I sleep soundly					
25	I feel depressed					
26	I feel I have the resources to deal with the difficulties of life					
27	When I feel the desire for something, I do everything to achieve it					
28	I follow closely the requirements of the doctor					

Addiction risk questionnaire. Rapid Indicators of Suspected Vulnerability to Addiction in patients with chronic pain (RISVA), by Claudio Leonardi, MD

Prevention and cure of chronic pain

- Literature is unanimous in supporting the role of physical exercise in the prevention of chronic pain of osteo-articular origin
- There is strong evidence for the effect of exercise on the pathogenesis of osteoporosis

Cochrane Database Syst Rev 2011,

- Multimodal therapy is the most efficent strategy

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Conclusion

- A balanced and early multimodal pain therapy including opioids as necessary:
  - Even in cases of acute pain
  - Improves quality of life of patients and helps to prevent neurological alterations
  - Contribute in preventing irreversible pain chronic syndromes with not negligible clinical and social implications
  - The follow-up is mandatory

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