

DOLORE CRONICO NELL' ANZIANO

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21-24 Novembre 2012

Vecchie e nuove strategie
terapeutiche: sicurezza ed
efficacia

Walter Gianni



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INRCA di Roma: "Tra due mesi si chiude, ma ancora non sappiamo dove andremo a lavorare"

Let's start.....

Older person's reflection about pain



*'I feel like a **dog thrown** in the middle of a street Anne Sutton, 85*

*It's shameful to live such a way **with little way of escape**. Over the years I have felt the loss of dignity and [been] left humiliated by pain.'*
Vanessa Wilson, 65

*"Living with pain" is a contradiction in terms. Why? If you are constantly in pain, **you don't have a life.**'* Vanessa Wilson, 65

*'There's **such humiliation** in pain.'* Claire Rayner, OBE, 76

*....but my chronic cancer pain is something which nobody really wants to know about and this results in a feeling of **'you're on your own'**.*
Annalise Sutton, 78

The main evidence about pain in elderly

Impact on

- Function
- Pain **MUST** be treated
- Sleep
- Impaired cognitive function
 - Quality of life



"Pain, whatever its source, is one of the most common complaints of the elderly" (Sarvis, 1995).



Fact and fiction about pain in the elderly

Myth: Pain is expected with aging.

Fact: Pain is not normal with aging. The presence of pain in the elderly necessitates aggressive assessment, diagnosis and management similar to younger individuals.

Myth: Pain sensitivity and perception decrease with aging.

Fact: Research is conflicting regarding age-associated changes in pain perception, sensitivity, and tolerance. Consequences of belief in this myth may mean needless suffering and under treatment of pain and underlying cause.

Myth: If an elderly person does not complain of much pain, they must not be in pain.

Fact: Older individuals may not report pain for a variety of reasons. They may fear the meaning of pain, diagnostic workups, or pain treatments. They may think pain is normal.



Myth: A person who appears to have no functional impairment and is occupied in activities of daily living must not have significant pain.

Fact: People have a variety of reactions to pain. Many individuals are stoic and refuse to “give in” to their pain. Over extended periods of time, the elderly may mask any outward signs of pain.

Myth: Narcotic medications are inappropriate for the elderly with chronic non-malignant pain.

Fact: Opioid analgesics are often indicated in non-malignant pain.

Myth: Potential side effects of narcotic medication make them too dangerous to use in the elderly.

Fact: Narcotics may be used safely in the elderly. Although the elderly may be more sensitive to narcotics, this does not justify withholding narcotics and failing to relieve pain.



What about management of pain in your patients?



I treat almost 70% of my patients with severe pain

What about your doctor's management of your pain?

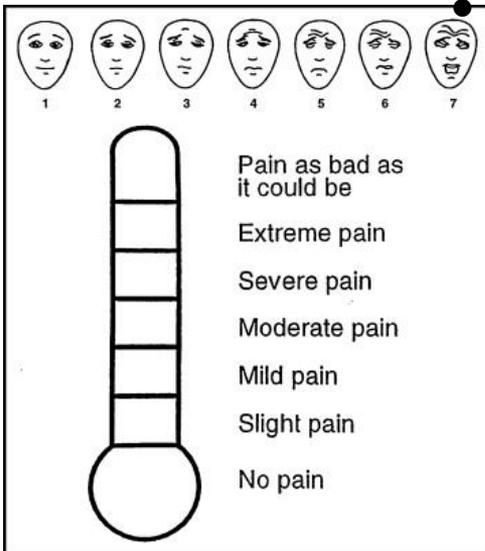


My doctor does not ask me about pain (1/3)

My doctor prevalently uses low dose opioids and NSAIDS

Types of pain in the elderly

- Nociceptive pain: Results from stimulation of pain receptors.
Somatic: damage to body tissue, well localized
Visceral: from viscera, poorly localized, may have nausea
- Neuropathic pain: Results from dysfunctions or lesions in either the central or peripheral nervous systems.
- Mixed pain syndromes: multiple or unknown mechanisms (e.g. headaches, vasculitic syndromes).
- Psychogenic Pain: somatoform disorders, conversion reactions.



Questions about pain in the elderly

*to treat
or not to treat?*



Management of Persistent Pain in Older Adults: The MOBILIZE Boston Study

Carrie Stewart, BSc, Suzanne G. Leveille, PhD,^{†‡§} Robert H. Shmerling, MD,^{§||}
Elizabeth J. Samelson, PhD,^{§**} Jonathan F. Bean, MD,^{††#} and Pat Schofield, PhD^{‡‡}*

OBJECTIVES: To describe the prevalence of pharmacological (PS) and nonpharmacological (NPS) pain management approaches used by older adults with persistent pain and to identify characteristics associated with use of these approaches.

DESIGN: Population-based cohort.

SETTING: Urban and suburban communities in the Boston, Massachusetts, area.

PARTICIPANTS: Seven hundred sixty-five adults aged 64 and older underwent a home interview and clinic examination. Those reporting any persistent pain were included in this analysis (N = 599).

MEASUREMENTS: All prescription and nonprescription medications were recorded during the home interview. NPS modalities for pain management were assessed using a modification of the Pain Management Inventory. The baseline assessment included extensive measures of pain, health, and functioning.

Table 1. Demographic and Health Characteristics According to Pain Management Strategy Among Older Adults with Persistent Pain: The MOBILIZE Boston Study

| Characteristic | All, N = 599 | No Pain Management Strategies, n = 120 | NPS, n = 185 | PS, n = 69 | PS and NPS, n = 225 | P-Value ^a |
|---|--------------|--|--------------|------------|---------------------|----------------------|
| Age, mean ± SD | 77.8 ± 5.3 | 77.3 ± 5.1 | 78.5 ± 5.6 | 77.5 ± 4.8 | 77.7 ± 5.3 | .06 |
| Female, n (%) | 400 (66.8) | 84 (56) | 115 (62.2) | 49 (71.0) | 170 (75.6) | .001 |
| White, n (%) | 460 (76.8) | 96 (80.0) | 141 (76.2) | 55 (79.7) | 168 (75.0) | .93 |
| Education ≥ 16 years, n (%) | 276 (46.1) | 60 (50.0) | 88 (47.6) | 21 (30.9) | 107 (47.6) | .15 |
| Self-reported health fair to poor, n (%) | 99 (16.5) | 15 (12.5) | 22 (11.9) | 13 (18.8) | 49 (21.8) | .02 |
| Obese, n (%) | 169 (28.2) | 44 (37.9) | 35 (19.3) | 24 (34.8) | 66 (30.1) | .02 |
| Chronic diseases, n (%) | | | | | | |
| Knee osteoarthritis | 181 (30.2) | 16 (13.3) | 55 (29.7) | 23 (33.3) | 87 (38.8) | <.001 |
| Rheumatoid arthritis | 36 (6.0) | 4 (3.3) | 12 (6.5) | 6 (8.7) | 14 (6.2) | .48 |
| Cancer | 144 (24.0) | 26 (21.7) | 42 (22.7) | 19 (27.5) | 57 (25.3) | .79 |
| Diabetes mellitus | 125 (20.9) | 24 (20.0) | 42 (22.7) | 17 (24.6) | 42 (18.7) | .64 |
| Heart disease | 151 (25.2) | 57 (47.5) | 75 (40.5) | 32 (46.4) | 86 (38.2) | .32 |
| Hospital anxiety and depression scale score, mean ± SD | 3.9 ± 3.0 | 3.2 ± 2.7 | 4.1 ± 3.0 | 4.2 ± 3.4 | 4.0 ± 2.9 | .006 |
| Chronic pain self-efficacy score <5.4, n (%) ^b | 132 (22.0) | 21 (21.9) | 32 (19) | 21 (33.9) | 58 (28.2) | .06 |
| Self-reported mobility difficulty | 230 (38.4) | 37 (30.8) | 57 (30.8) | 30 (43.5) | 106 (47.1) | .002 |
| Activity of daily living difficulty | 151 (25.2) | 24 (20.0) | 36 (19.5) | 20 (29.0) | 71 (31.6) | .02 |
| Brief pain inventory | | | | | | |
| Severity | | | | | | |
| Very mild | 210 (35.1) | 68 (56.7) | 78 (42.2) | 17 (24.6) | 47 (20.9) | |
| Mild | 200 (33.4) | 35 (29.2) | 62 (33.5) | 27 (39.1) | 76 (33.8) | |
| Moderate to severe | 189 (31.6) | 17 (14.2) | 45 (24.3) | 25 (36.2) | 102 (45.3) | <.001 |
| Interference | | | | | | |
| None | 125 (20.9) | 51 (42.5) | 42 (22.7) | 16 (23.2) | 16 (7.1) | |
| Low | 144 (24.0) | 35 (29.2) | 54 (29.2) | 8 (11.6) | 47 (21.0) | |
| Medium | 162 (27.0) | 19 (15.8) | 50 (27.0) | 18 (26.1) | 75 (33.5) | |
| High | 167 (27.9) | 15 (12.5) | 39 (21.1) | 27 (39.1) | 86 (38.4) | <.001 |

Table 2. Predictors of Pain Management Approach Used by Older Adults with Persistent Pain (N = 599)

| Predictors | NPS, n = 180 | PS, n = 69 | PS and NPS, n = 213 |
|--|------------------------------|------------------------------|------------------------------|
| | OR (95% Confidence Interval) | OR (95% Confidence Interval) | OR (95% Confidence Interval) |
| Female | 1.23 (.73–2.07) | 1.66 (.84–3.3) | 2.2 (1.26–3.82) |
| Fair or poor health | .56 (.23–1.36) | .56 (.2–1.59) | .52 (.22–1.21) |
| Body mass index \geq 30.0 kg/m ² (reference < 25.0 kg/m ²) | .29 (.15–.56) | .67 (.29–1.56) | .46 (.23–.91) |
| Knee osteoarthritis | 2.64 (1.37–5.07) | 2.41 (1.11–5.22) | 3.07 (1.6–5.88) |
| Hospital Anxiety and Depression Scale score | 1.06 (.96–1.16) | 1.02 (.91–1.14) | .98 (.89–1.08) |
| Brief pain inventory | | | |
| Severity (reference very mild) | | | |
| Mild | 1.48 (.82–2.68) | 2.48 (1.12–5.49) | 2.37 (1.27–4.45) |
| Moderate to severe | 2.36 (1.05–5.32) | 3.29 (1.21–8.94) | 5.02 (2.23–11.28) |
| Interference (reference none) | | | |
| Low | 1.60 (.86–3.0) | .69 (.26–1.83) | 4.08 (1.91–8.69) |
| Moderate | 2.19 (1.02–4.69) | 2.37 (.92–6.12) | 9.68 (4.15–22.56) |
| High | 1.72 (.68–4.35) | 3.27 (1.11–9.6) | 8.58 (3.22–22.85) |

Multinomial logistic regression models using forward stepwise selection ($P < .05$). All odds ratios (ORs) in comparison to those reporting no pain management.

NPS = nonpharmacological; PS = pharmacological.

CONCLUSION

This study has found that a small proportion of older adults (~one-third) who report persistent pain are using pain management strategies consistent with current geriatric guidelines. Use of NPS strategies by older adults with pain is common and may reflect the general avoidance of recommendations or prescriptions for PS strategies by healthcare providers caring for older adults. Substantial differences exist in the characteristics of those who use individual strategies, and these findings may inform future research in this area. Future studies should build upon existing knowledge of older people's preferences for pain management strategies to facilitate better adherence and targeting of pain management interventions for older adults living in the community. Clinicians should consider the potential influences of older adults' preferences and experiences with pain management when recommending pain management strategies.



Barriers to effective pain management

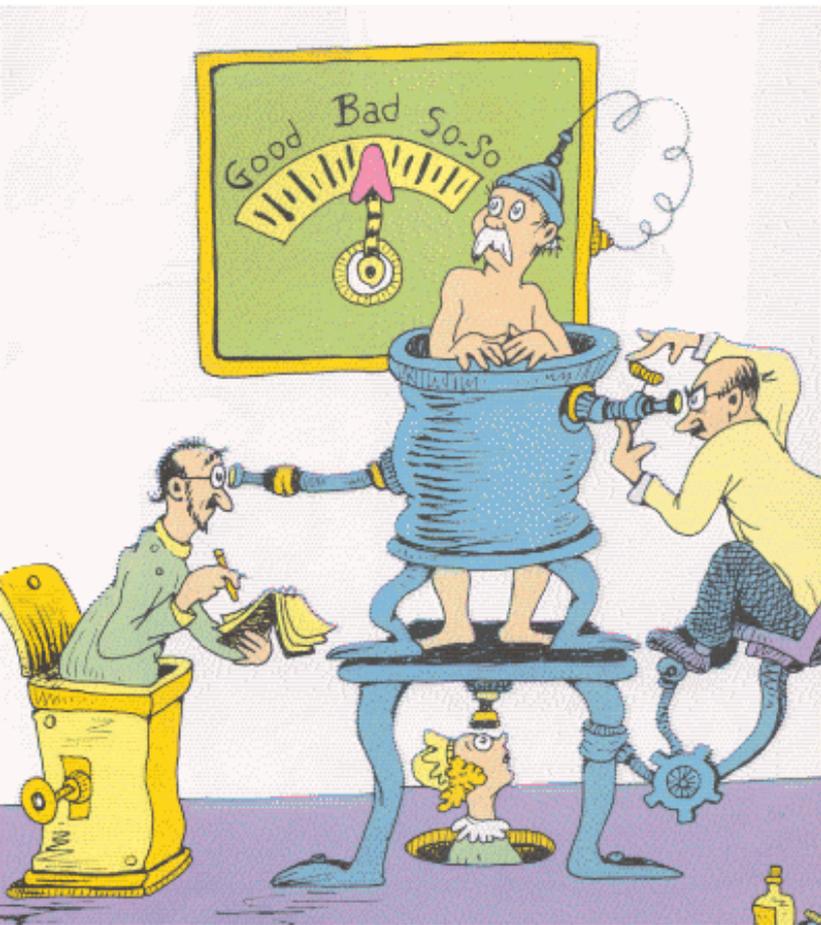


Study of 805 chronic pain sufferers, >50% changed physicians due to lack of physician's:

- 1) Willingness to treat the pain aggressively,
- 2) Failure to take the pain seriously,
- 3) Lack of knowledge about pain management



"A stabbing pain, you say?"



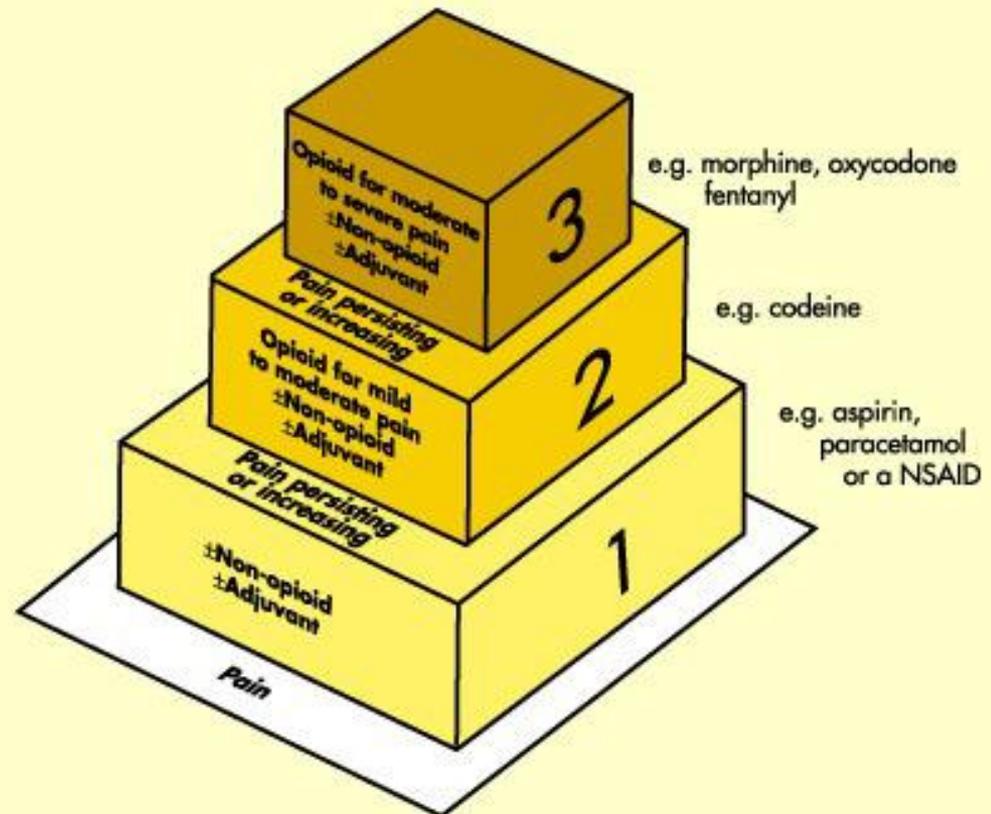
The most reliable indicator of the existence pain and its intensity is the patient's description.

Questions about pain in the elderly

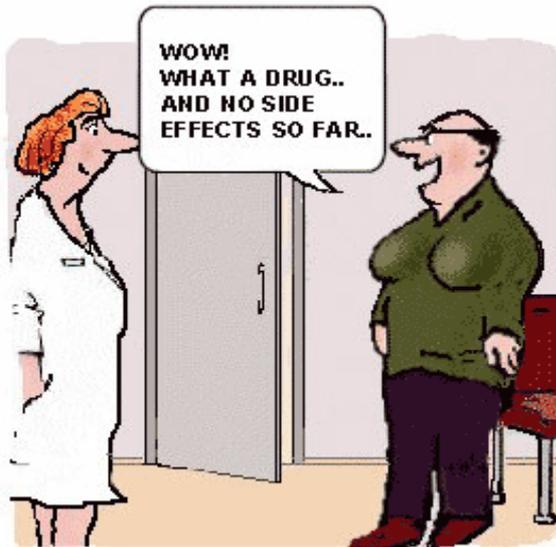
How to treat?



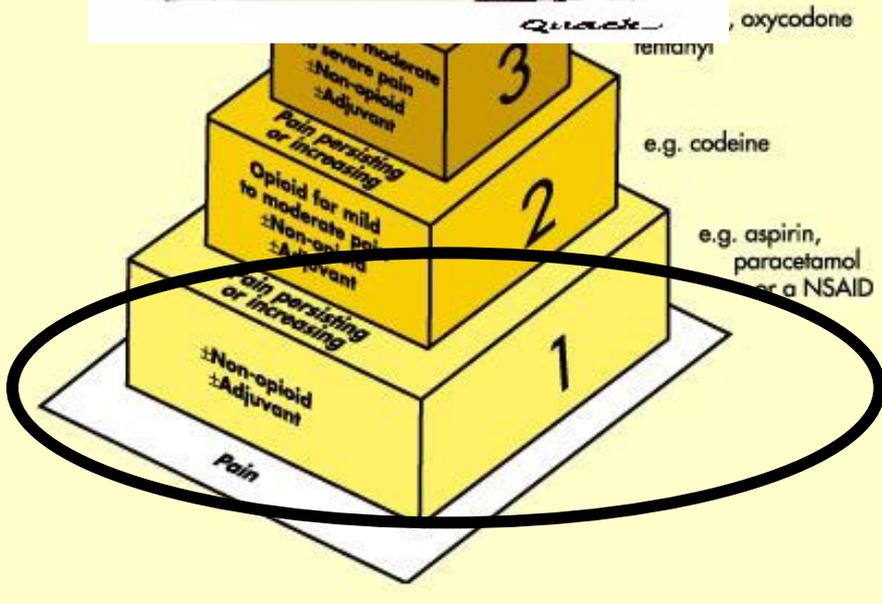
The three step ladder for pain relief



The first step for pain relief in elderly



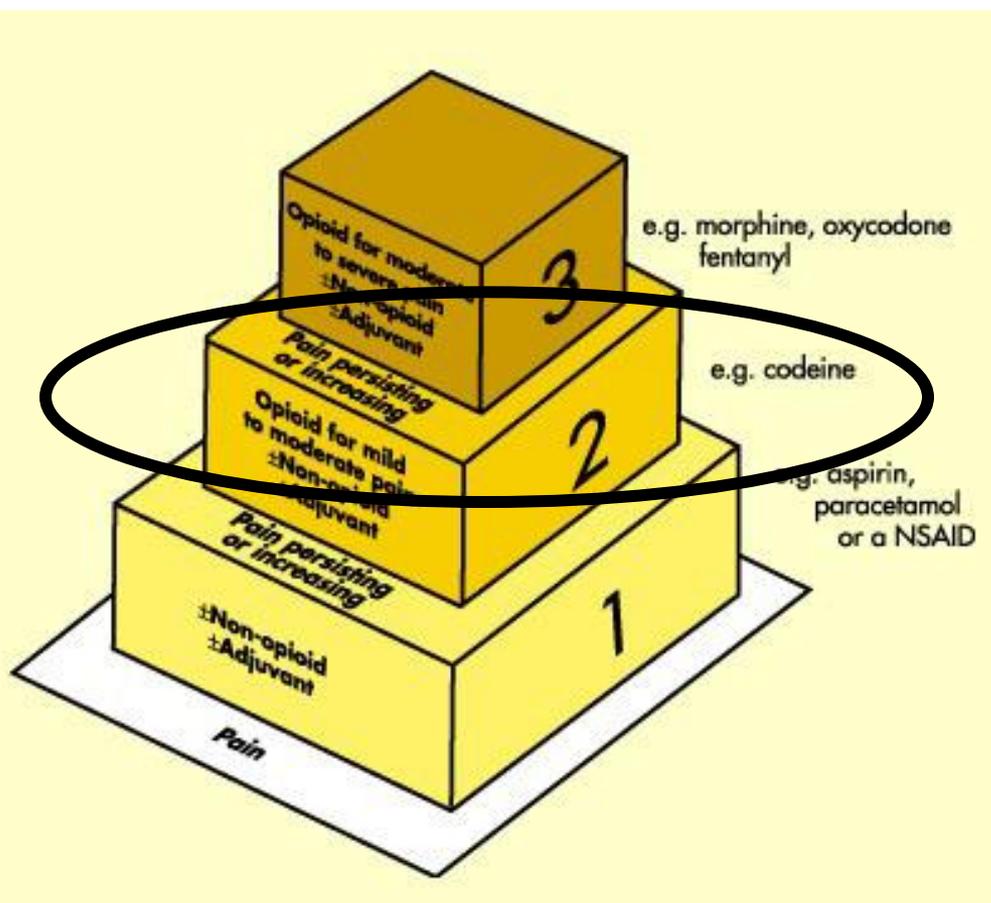
All of these drugs have a ceiling effect and NSAIDs are noted for possible **side effects** including gastrointestinal ulceration/bleeding, renal impairment, salt/fluid retention and exacerbation of heart failure. **The elderly are at an increase risk for these side effects.**



The American Geriatric Society guidelines highlight the probability that long-term NSAID use is associated with greater adverse events than long-term opioid use.

Consequently, they have suggested **introduction of opioid analgesia early in the course of cancer related pain.**

The second step for pain relief in elderly

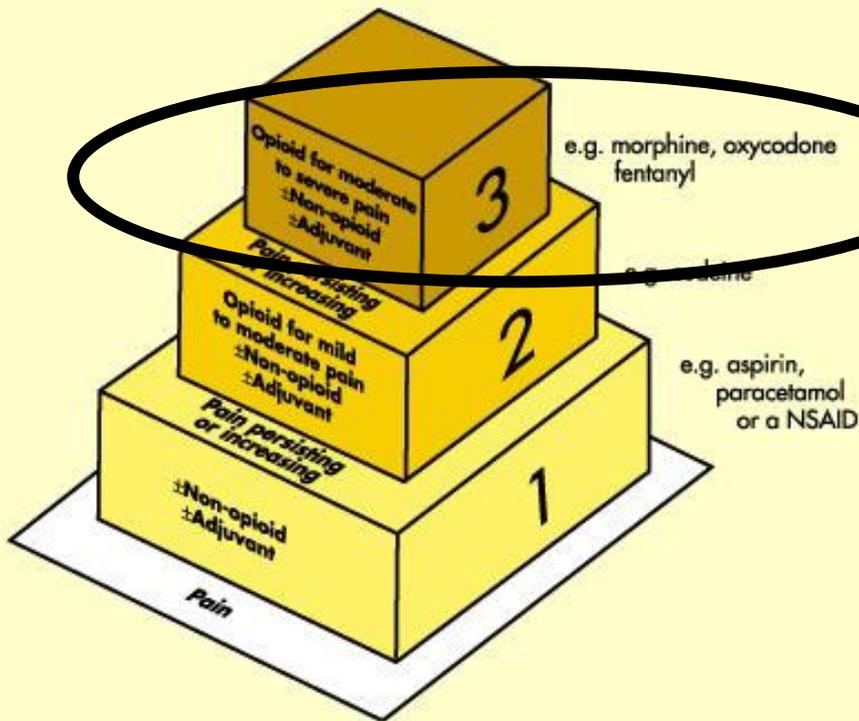


There are proponents for **skipping this step**, arguing that cancer pain of moderate intensity should be immediately treated with Step 3 opioids.

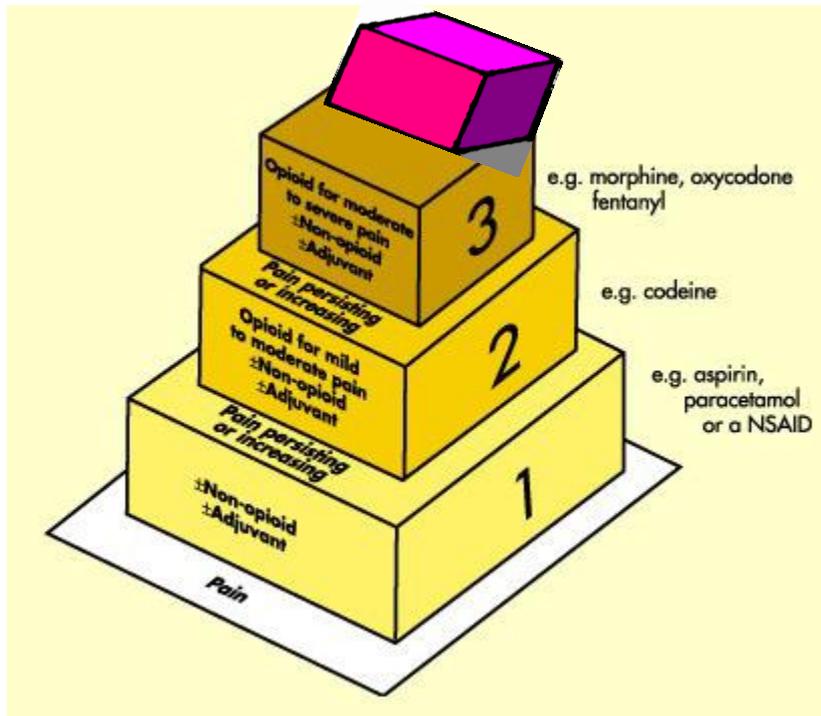
Reasons: tramadol induces serious stipsis
Codein, other than its known side effects, is not metabolized by 10% of Caucasian population

The third step for pain relief in elderly

- Chronic cancer pain frequently requires strong opioids and this is **no exception in the elderly.**
- Due to pharmacokinetic and physiological changes in the elderly, the titration of opioids in the elderly should be undertaken with greater caution.
 - . A prudent approach is to begin with an immediate release opioid and slowly titrate according to analgesia and side effects.
- There is no ceiling dose for opioids, with doses being limited by side effects alone
- . If intolerable side effects occur, consider switching to another opioid
- Another option is to add adjuvant analgesics or non-opioid analgesics in an attempt to decrease the opioid dose while maintaining adequate analgesia.



The fourth step for pain relief in elderly



- 'Step 4' of the WHO analgesic step ladder is considered when there is inadequate response to step 3 agents, due either to inadequate pain control or inability to tolerate the step 3 agents
- These treatment options include the use of nerve blocks, as well as spinal administration of local anaesthetics, opioids and other adjuvants.
- Oral administered ketamine

Adjuvant drugs

- Duloxetine and pregabalin in neuropathic pain
 - Corticosteroids
 - Tricyclic Antidepressants
- Selective Serotonin Reuptake inhibitors
 - Bisphosphonate
 - Topical analgesic

Proper application of these guidelines can lead to effective analgesia in 90% of cases...but...

Unique Aspects of Analgesic Therapy in the Elderly have to be considered

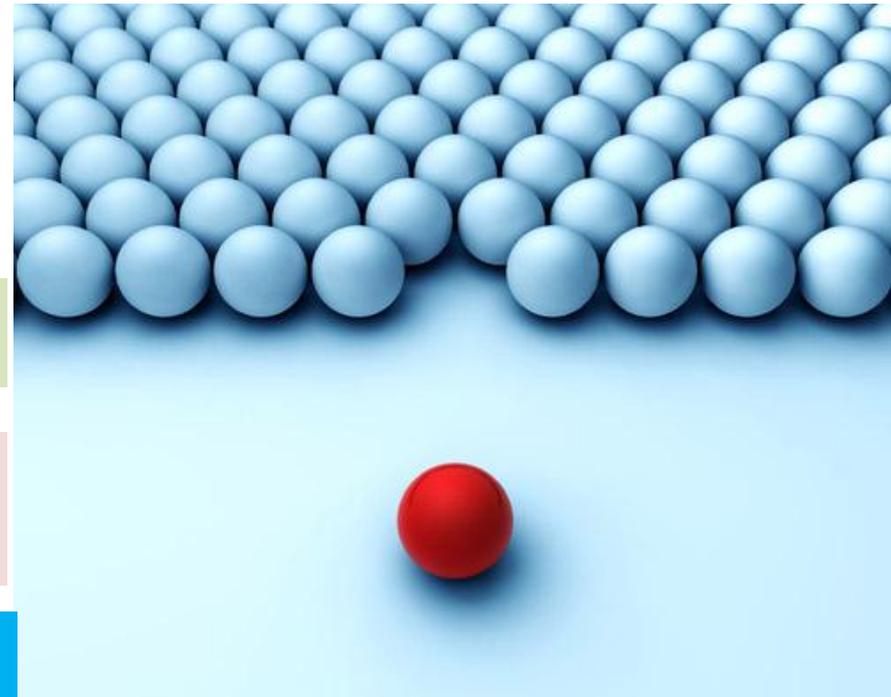
decreased renal and hepatic function

changes in body fat that lead to increases in the distribution of lipid soluble analgesics

changes in volume of distribution that increases the effect of hydrophilic drugs

decreased salivary production, making administration of sublingual and transmucosal formulations challenging

decreased peristalsis, predisposing the elderly to opioid-related constipation



And now a little about opioids...

- Bind to one or more of the opiate receptors (mu, kappa, delta)
- Mu receptor is 7 transmembrane G protein coupled receptor
 - binding stabilizes the membrane so neuron doesn't fire
- Where are the mu receptors?
 - periphery, dorsal root ganglia of spinal cord, periaqueductal grey of brainstem, midbrain, gut

Pain Management and Older Adults

- Need frequent re-assessment
 - effectiveness of analgesia
 - ADLs/ functional status
 - adverse effects
 - constipation
 - ? unusual behaviors
 - may be a sign of an adverse drug effect

Is there any evidence that one opioid is better than another?

- ❑ Evidence of some differential stimulation of opiate receptors among opioids.
- ❑ Good clinical evidence lacking so far about clinical significance of these differences.
- ❑ Also limited clinical evidence about differences in adverse effect profiles between different opioids.

The best opioid should:



avoid constipation

avoid other drugs interactions

Which opioid???

- Naloxone -oxycodone in association





For Healthcare Professional Media Only
Embargo: 00.01, 26 January 2009

For Medical Media Only

Not intended for media in Austria, Denmark, Iceland, Norway, Sweden, UK, France, Czech Republic and Switzerland

***Targin*[®] (oral oxycodone/naloxone prolonged-release tablet) now launching across Europe to control severe chronic pain with significantly reduced risk of opioid-induced constipation**

First analgesic therapy to combine oxycodone, a strong opioid, with naloxone, an opioid antagonist, offers a new treatment option for physicians



The Phase III clinical trial programme, which included 1,064 patients, demonstrated that Targin provides equivalent pain relief to prolonged-release oxycodone alone, whilst significantly reducing the risk of opioid-induced constipation.

Targin has also been proven to provide pain relief that lasts for up to 12 hours from the first dose.



Mechanism of Action

Oxycodone and naloxone have an affinity for kappa, mu and delta opiate receptors in the brain, spinal cord and peripheral organs (e.g., intestine). Oxycodone acts as opioid-receptor agonist at these receptors and affects pain relief by binding to the endogenous opioid receptors in the CNS. Oxycodone acts on the gut opioid receptors and induces constipation. Naloxone is a pure antagonist acting on all types of opioid receptors. Naloxone acts locally on the gut opioid receptors and counteracts the opioid-induced constipation.

Because of the extensive first-pass metabolism in the liver, the bioavailability of naloxone upon oral administration is <3%, therefore a clinically relevant systemic effect is unlikely. Due to the competitive antagonism of the opioid receptor mediated oxycodone effect by naloxone in the gut, naloxone's local opioid antagonist effect reduces the constipation that is typical with opioid treatment.

Opioids can influence the hypothalamic-pituitary-adrenal or gonadal axes. Among the changes observed are an increase of prolactin in the serum and a reduced level of cortisol and testosterone in the plasma. Clinical symptoms may occur because of these hormone changes.



Geriatrics (> 65 years of age):

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease and other drug therapy.

The dosage should be adjusted to the intensity of the pain and the sensitivity of the individual patient.

RESEARCH ARTICLE

Open Access

Efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials

Oliver Löwenstein¹, Petra Leyendecker^{2*}, Eberhard A Lux³, Mark Blagden⁴, Karen H Simpson⁵, Michael Hopp², Biörn Bosse², Karen Reimer^{2,6}

Abstract

Background: Two randomised 12-week, double-blind, parallel-group, multicenter studies comparing oxycodone PR/naloxone PR and oxycodone PR alone on symptoms of opioid-induced bowel dysfunction in patients with moderate/severe non-malignant pain have been conducted.

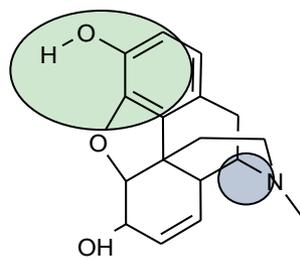
Methods: These studies were prospectively designed to be pooled and the primary outcome measure of the pooled data analysis was to demonstrate non-inferiority in 12-week analgesic efficacy of oxycodone PR/naloxone PR versus oxycodone PR alone. Patients with opioid-induced constipation were switched to oxycodone PR and then randomised to fixed doses of oxycodone PR/naloxone PR (n = 292) or oxycodone PR (n = 295) for 12 weeks (20-80 mg/day).

Results: No statistically significant differences in analgesic efficacy were observed for the two treatments (p = 0.3197; non-inferiority p < 0.0001; 95% CI -0.07, 0.23) and there was no statistically significant difference in frequency of analgesic rescue medication use. Improvements in Bowel Function Index score were observed for oxycodone PR/naloxone PR by Week 1 and at every subsequent time point (-15.1; p < 0.0001; 95% CI -17.3, -13.0). AE incidence was similar for both groups (61.0% and 57.3% of patients with oxycodone PR/naloxone PR and oxycodone PR alone, respectively).

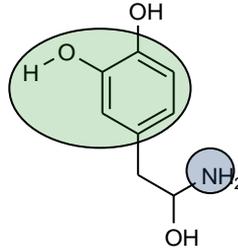
Conclusions: Results of this pooled analysis confirm that oxycodone PR/naloxone PR provides effective analgesia and suggest that oxycodone PR/naloxone PR improves bowel function without compromising analgesic efficacy.

Trial registration numbers: ClinicalTrials.gov identifier: NCT00412100 and NCT00412152

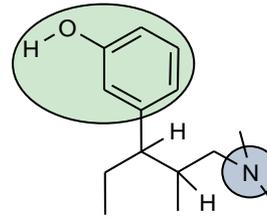
Tapentadol: “more than MOR”



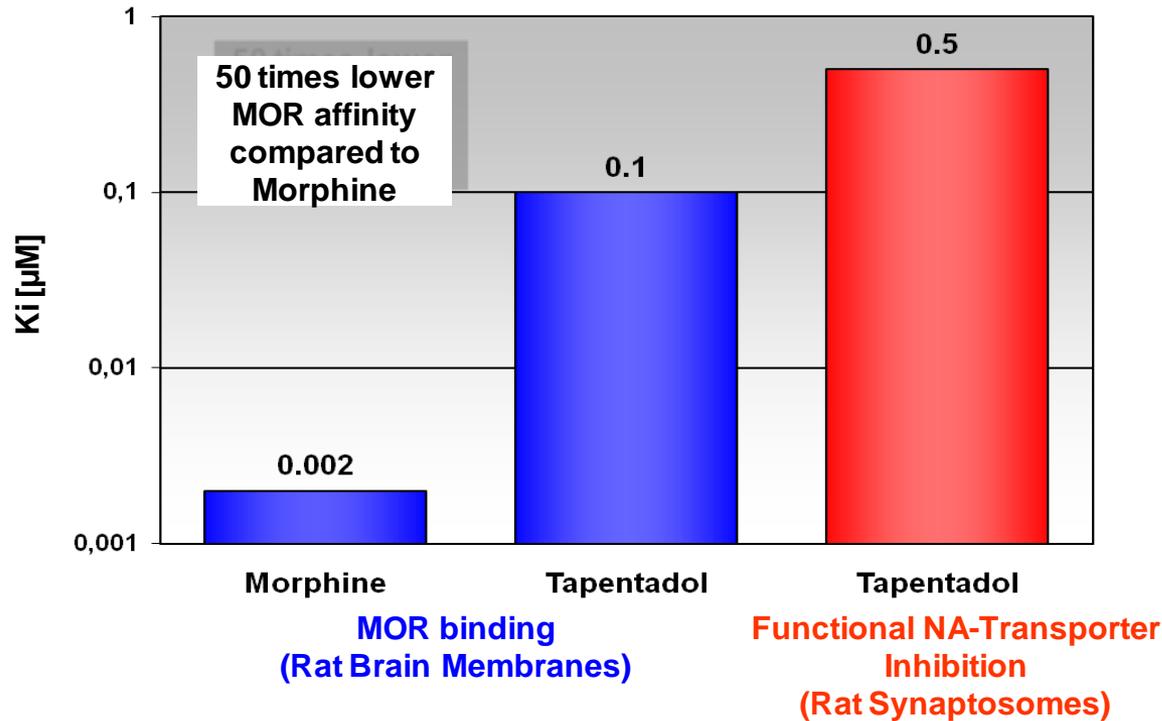
Morfina



Noradrenalina



Tapentadolo



[Drugs Aging](#). 2012 Aug 1;29(8):615-25. doi: 10.2165/11632620-000000000-00000.

Treatment of chronic pain in older people: evidence-based choice of strong-acting opioids.

van Ojik AL, Jansen PA, Brouwers JR, van Roon EN.

Expertise Centre for Pharmacotherapy in Old Persons (Ephor), University Medical Center, Utrecht, The Netherlands.

Abstract

In the treatment of chronic malignant and non-malignant pain, opioids are used as strong analgesics. Frail elderly patients often have multiple co-morbidities and use multiple medicines, leading to an increased risk of clinically relevant drug-drug and drug-disease interactions. Age-related changes and increased frailty may lead to a less predictable drug response, increased drug sensitivity, and potential harmful drug effects. As a result, physicians face a complex task in prescribing medication to elderly patients. In this review, the appropriateness of the strong-acting opioids buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone and tapentadol is determined for use in elderly patients. Evidence-based recommendations for prescribing strong opioids to the frail elderly are presented. A literature search was performed for all individual drugs, using a validated and published set of 23 criteria concerning effectiveness, safety, pharmacokinetics and pharmacodynamics, experience, and convenience in elderly patients. First, information on the criteria was obtained from pharmaceutical reference books and a MEDLINE search. The information obtained on the individual drugs in the class of opioids was compared with the reference drug morphine. Evidence-based recommendations were formulated on the basis of the pros and cons for the frail elderly. Using the set of 23 criteria, no differentiation can be made between the appropriateness of buprenorphine, fentanyl, hydromorphone, morphine and oxycodone for use in elderly patients. Methadone has strong negative considerations in the treatment of chronic pain in the frail elderly. Methadone has a high drug-drug interaction potential and is associated with prolongation of the QT interval and a potential risk of accumulation due to a long elimination half-life. In addition, methadone is difficult to titrate because of its large inter-individual variability in pharmacokinetics, particularly in the frail elderly. ~~Because of a lack of empiric knowledge, the use of tapentadol is not recommended in frail elderly persons.~~ Nevertheless, tapentadol may prove to be a useful analgesic for the treatment of chronic pain in frail elderly persons because of its possible better gastrointestinal tolerability. In the treatment of chronic pain in the frail elderly, the opioids of first choice are buprenorphine, fentanyl, hydromorphone, morphine and oxycodone. In order to improve the convenience for elderly patients, the controlled-release oral dosage forms and transdermal formulations are preferred.

PMID: 22765848 [PubMed - in process]

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Post hoc analyses of data from a 90-day clinical trial evaluating the tolerability and efficacy of tapentadol immediate release and oxycodone immediate release for the relief of moderate to severe pain in elderly and nonelderly patients

Gary Vorsanger PhD MD¹, Jim Xiang PhD¹, David Biondi DO¹, David Upmalis MD²,
Jacqueline Delfgaauw PhD³, René Allard PhD⁴, Bruce Moskowitz MD¹

RESULTS:

Data from 849 patients randomly assigned (4:1 ratio) to treatment with a study drug (tapentadol IR [n=679] or oxycodone IR [n=170]) were analyzed according to age (younger than 65 years of age [nonelderly], or 65 years of age or older [elderly]) and treatment group. Among elderly patients, incidences of constipation (19.0% versus 35.6%) and nausea or vomiting (30.4% versus 51.1%) were significantly lower with tapentadol IR versus oxycodone IR (all $P < 0.05$). Initial onsets of nausea and constipation occurred significantly later with tapentadol IR versus oxycodone IR (both $P \leq 0.031$). Tapentadol IR-treated elderly patients had a lower percentage of days with constipation than oxycodone IR-treated patients ($P = 0.020$). For tapentadol IR- and oxycodone IR-treated elderly patients, respectively, incidences of study discontinuation due to gastrointestinal treatment-emergent adverse events were 15.8% and 24.4% ($P = 0.190$). Tapentadol IR and oxycodone IR provided similar pain relief, with no overall age-dependent efficacy differences (mean pain scores [11-point numerical rating scale] decreased from 7.0 and 7.2 at baseline, to 4.9 and 5.2 at end point, respectively).

CONCLUSIONS: Tapentadol IR was safe and effective for the relief of lower back pain and osteoarthritis pain in elderly patients, and was associated with a better gastrointestinal tolerability profile than oxycodone IR.

Key Words: Analgesia; Elderly; Opioid; Pain management; Tapentadol IR

Tolerability of tapentadol IR in elderly and nonelderly patients

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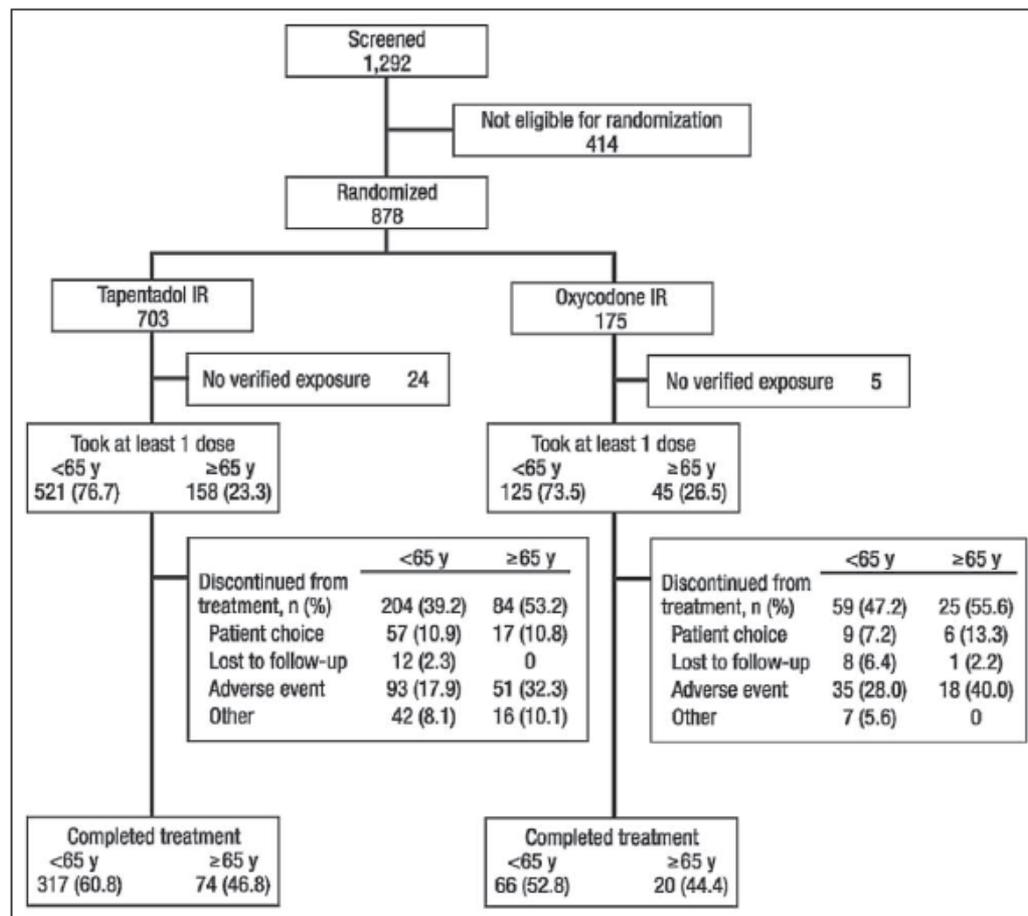
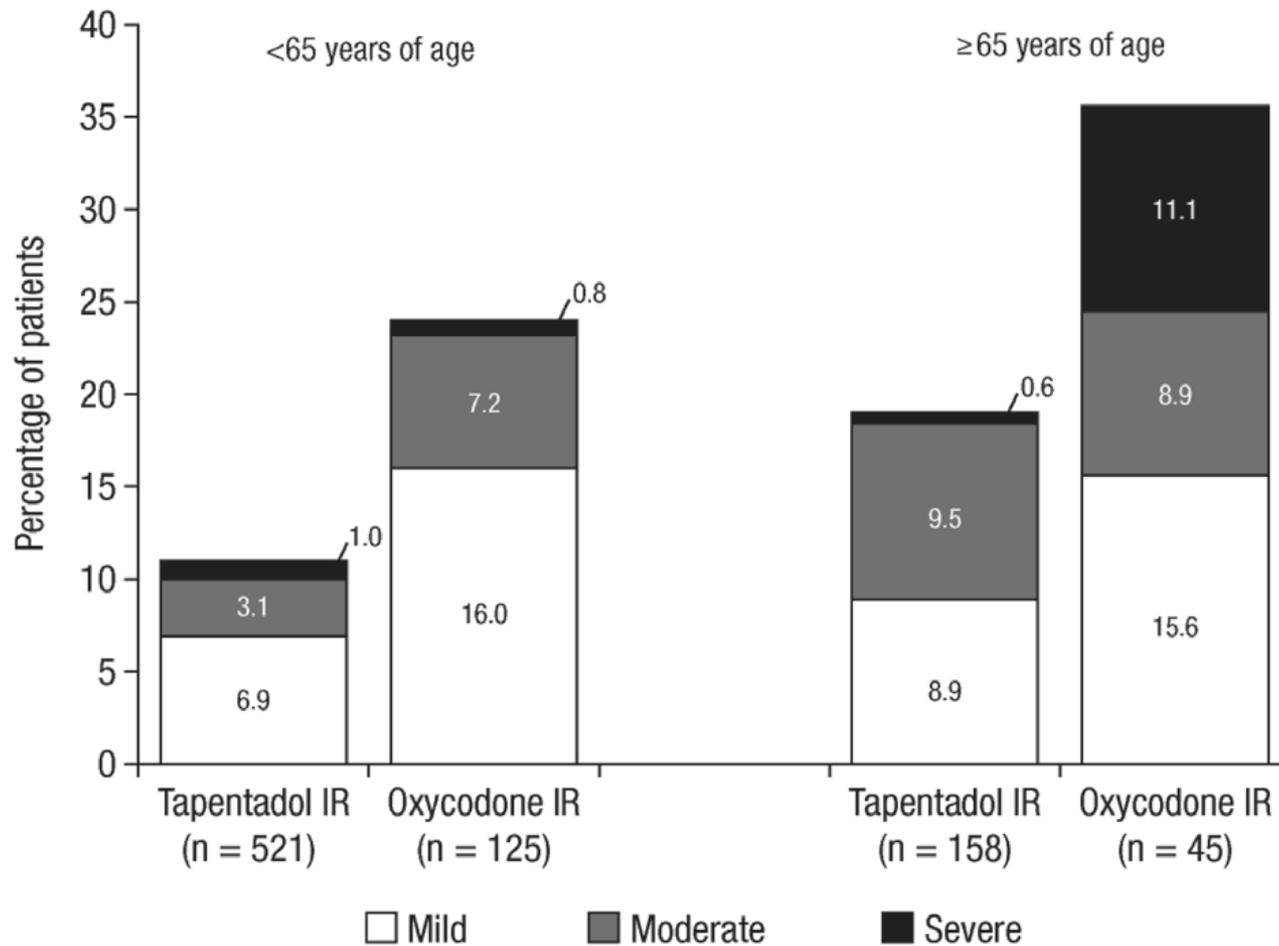


Figure 1) Patient disposition. Data presented as n (%) unless otherwise indicated. IR Immediate release; y Years of age. Adapted with permission from Informa Healthcare (reference 32)



Incidence of constipation according to intensity, age group and treatment

Non-drug treatment

- Cognitive-behavioral therapy: Pain is influenced by cognition, affect and behavior.

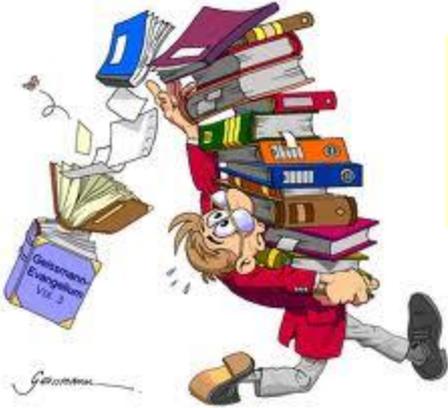
Conducted by a trained therapist, focuses on changing individual cognitive activity to modify associated behavior, thoughts, and emotions.

10-12 weekly individual or group sessions

Participants have to be cognitively intact

- Operant behavior therapy: Use of negative and positive consequences to modify the behaviors.
- Mind-body conditioning practices: Yoga, tai chi, qigong.

Take home message



- 1) Avoid the use of NSAIDs and selective COX-2 inhibitors.
- 2) Weak opioids are characterized by extreme variability in response rate as well as a poor toxicity profile
- 3) We suggest the use of strong opioids at low starting doses, administered orally according to all international guidelines. Transdermal formulations are not recommended as first choice due to the variability in cutaneous drug absorption.
- 4) To date, the most solid evidence supports the use of oxycodone and transdermal buprenorphine (in patients with renal failure)
- 5) Results from ongoing studies on oxycodone-naloxone combination and tapentadol are awaited. Due to their favorable pharmacological profile, these drugs may improve the therapeutic strategy in this particular subset of patients.

I CAN'T
STAND IT!



Thanks for attention