PRC

Challenges posed by cancer pain clinical trials

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Cancer pain

Inter-individual variability

Pain relief

Clinical trials

- Test an hypothesis or answer a research question
  - Is drug A better than drug B ?
  - Is Drug A better than placebo ?
  - Is drug A equally effective to drug B ?
  - …..

Cancer Pain Trials Design

- Parallel arm RCT
- Cross Over RCT
- Enriched trial design
- Observational

Pain measurement requires subjective assessment scales

- 0 – 10 Numerical scales
- Visual analogue scales
- Verbal scales

Analgesic clinical trials in chronic pain

Type of bias	Cancer pain
Selection bias	High variability (random)
Performace	Blinding and placebo
Attitrion	Often very high
Duration	Short is better (?) 4 week
Imputation	No difference
Size	100 to 200 patients for study arm (?)

from Moore et al Br J Anaesh 2013

Patients selection - not only randomization

- Can individual variability in cancer pain be reduced ?
  - Pain type patient characteristics
    - Nociceptive
    - Neuropathic
    - Pain changes over time due to disease
    - Psychological
  - Opiod exposure
  - Concurrent medication
  - Concurrent anticancer treatment

Pain characteristics

- BTP /incident
- Pain intensity
- neuropathic pain
- Psycological distress
- localisation of pain,
- non-opioids
- Sleep
- addiction,
- cancer diagnosis
- localisation of metastases
- age

Knudsen AK 2010
Brunelli 2014

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PAIN

Classification of neuropathic pain in cancer patients: A Delphi expert survey report and EAPC/IASP proposal of an algorithm for diagnostic criteria

Cinzia Brunelli [1,2,*], Michael I. Bennett [3], Stein Kaasa [4,5], Robin Fainsinger [6], Per Sjøgren [7], Sebastiano Mercadante [8], Erik T. Lehrer [9,10], Augusto Caraceni [11,*], on behalf of the European Association for Palliative Care (EAPC) Research Network, the International Association for the Study of Pain (IASP) Cancer Pain Special Interest Group

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Placebo response

- The comparison of an investigational treatment with placebo is considered the gold standard for assessing efficacy and safety when a delay in the onset of treatment does not cause any lasting adverse effects and assuming that subjects fully understand their right to withdraw from the trial at any time for any reason

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Blinding

- In general blinding becomes more important to reduce “assessor bias” as the outcomes become more subjective
- unblinded patients increase the size of the effect by an average of 0.56 SD

Hròbjartsson A. et al Int J Epidemiol 2014

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Defining the outcome

- Mean pain score
- % patients reaching significant pain relief (30% 50%)
- Time – duration

- Patient satisfaction
- Quality of life

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Endpoints longitudinal data and summary measures

- Short term
- Long term

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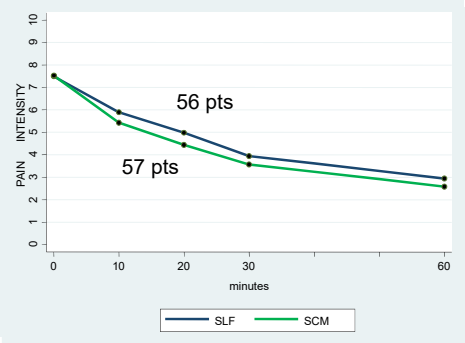
Pain intensity trend acute administration



Zecca et al JCO in press

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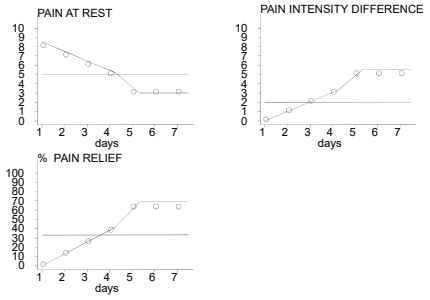
How to summarize pain controll over time



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Outcome = time to reach stable pain control

Stable pain control = receiving less than 3 breakthrough pain doses per day pain </= 3 for three consecutive days

Fainsinger R et al Eur J Cancer 2010

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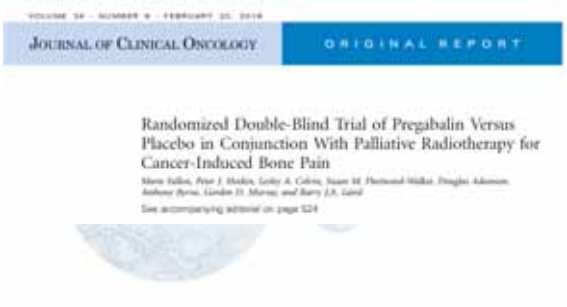
Pregabalin and bone pain


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Double-Blind Trial of Pregabalin Versus Placebo in Conjunction With Palliative Radiotherapy for Cancer-Induced Bone Pain

Marie Fallon et al 2015

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Inclusion criteria and outcome

- 1970 screened 233 allocated to study randomization
- Worst pain >/= 4 over 10
- Endpoint reduction of 2 points from baseline with reduced or stable opioid dose

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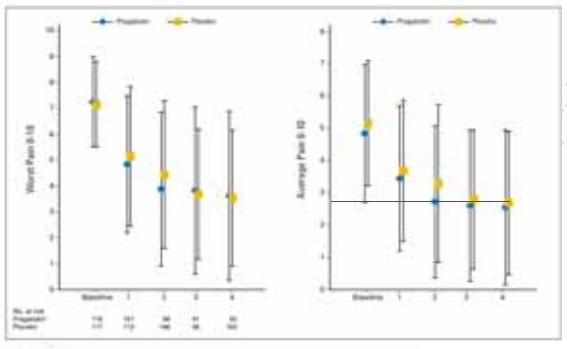
Responders = 38.8% pregabalin 40.2% placebo



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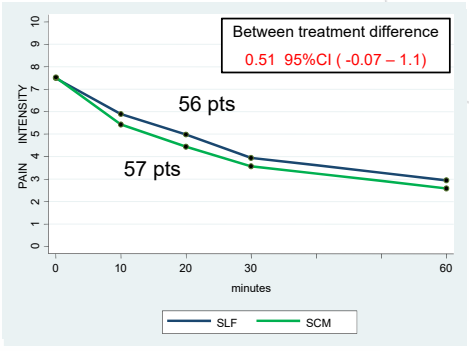
Pain intensity trend acute administration



Zecca et al JCO in press

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Pain score analysis (ANCOVA) during the whole treatment period (average values)

	GLOBAL PAIN	SHOOTING PAIN	BURNING PAIN	DYSESTHESIAS	EPISODES OF LANCINATING PAIN
Gabapentin	4.7 (1.9)	3.8 (2.4)	2.4 (2.1)	4.5 (2.3)	3.5 (4.3)
Placebo	5.9 (2.1)	4.4 (3.0)	2.8 (2.7)	5.2 (2.2)	7.8 (15.6)
P	0.0250	0.1988	0.6809	0.0077	0.9930

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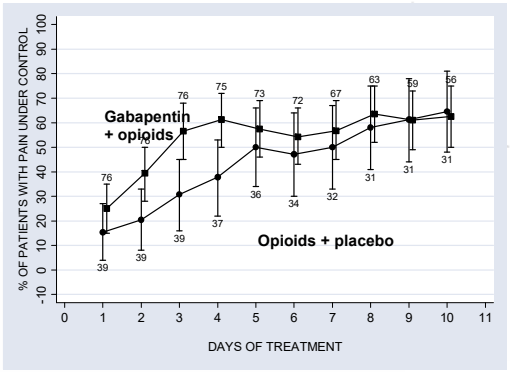

Caraceni et al JCO 2004

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- Individual variability patients selection
- Outcome choice
- Clinical interpretation of the results

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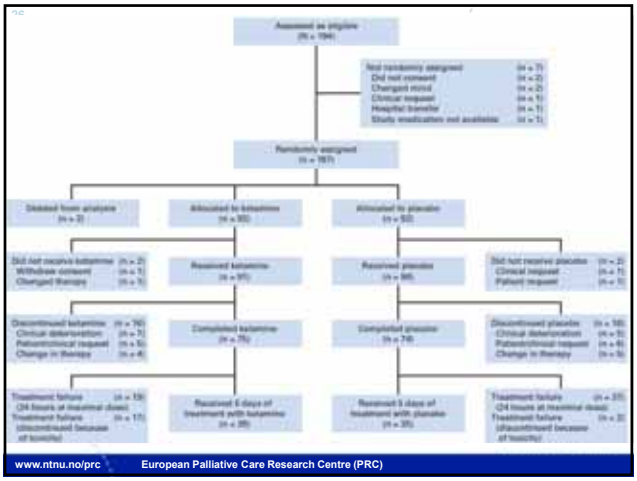
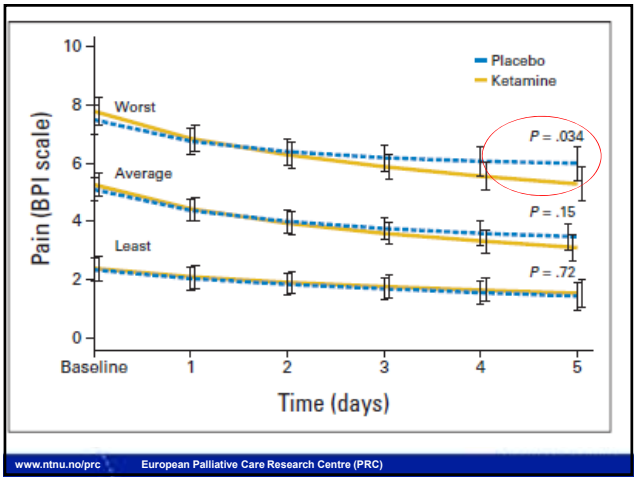
Patients and outcome

- Patient with pain >/= 3
- Endpoint reduction of 2 points with no more than 4 doses of breakthrough analgesics in 24 hours
- Opiods stable but access to breakthrough doses
- Responder analisis no difference





Toxicity as an objective of analgesic clinical trials

- How to measure ?
- One example
  - any worsening of at least 2 points on a 0 to 10 NRS during 14 days treatment period on any side effect out of 7 chosen among opiod side effects

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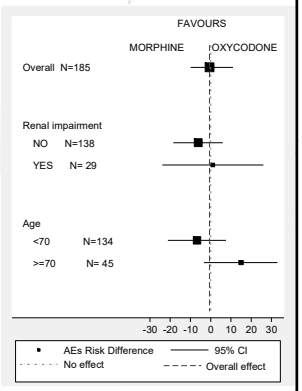
Outcomes - Adverse Events

Morphine	Oxycodone
84.0%	84.6%

Risk Difference
-0.6%

95%CI
-11.0 % to 9.9%

187 enrolled – 400 planned



Zecca et al JPSM in Press

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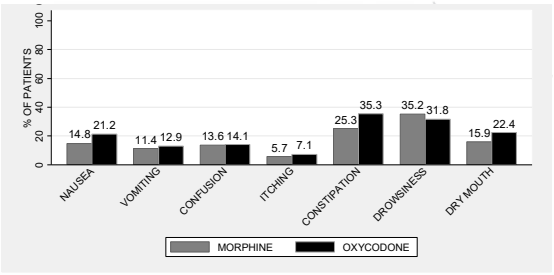
Results - Adverse event profile % of patients reporting any 2 point worsening during 14 days follow up



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How does pain look like to patients?

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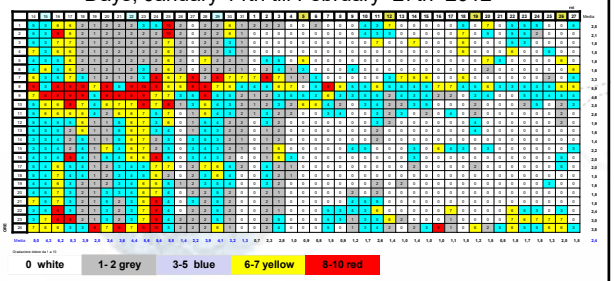
Days, January 14th till February 27th 2012



Pain colour code scale

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Sarà futuro?

- Il ghiaccio infernale della solitudine
  si scioglie con rabbia di fronte
  ad una mano tesa.
- Il fuoco insaziabile di una croce agonizza
  e si affievolisce lentamente all' arrivo
  del bagliore di un sorriso
- L'ossessione di sepolcrali pensieri inizia
  a strozzare se stessa non appena giunge
  la prima nota di un canto nuovo:
  la speranza

Lara Gastaldello a chordoma patient 1998

"The Ice from hell and loneliness melts in front of an open hand"

"The hungry Fire of an agonizing cross calms down slowly when a smile comes"

"The obsession of deadly thoughts starts to drawn as soon as it comes the first note of a new song : hope "