Opioid resistant pain – Evidence-based Clinical Aspects

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From Melzack and Wall Textbook of Pain 3rd ed 1995

Chapter 49 “Opioids” Robert Twycross

Opioid Resistant Pain

“ All pain is not equally responsive to opioid analgesics. It is useful to have a working classification of pain based on anticipated response to opioids” (Table 49.3)

Table 49.3 Opioid Resistant Cancer pain Classification

Pseudo-resistant

- underdosing
- poor absorption
- poor intake
- ignoring psychological aspects of care

Semi-resistant

- Bone metastases
- Neuropathic (Some)
- RICP
- Activity related

Resistant

- Neuropathic (some)
- Muscle spasm

Pain 33 (1988) 11-23

Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain

S. Arnér and B.A. Meyerson

Departments of Anesthesiology and Neurosurgery, Karolinska Hospital, S101 01 Stockholm (Sweden)

(Received 9 November 1987, revision received 5 January 1988, accepted 7 January 1988)

Main message: nociceptive, idiopathic and neuropathic pains respond differently to opioids. Neuropathic pain is insensitive to opioids

"Some patients were …pleased to understand that lack of true analgesic effect [from the i.v. opioid test] indicated the futility of continuous use…."

"Opioid-responsive and opioid-non-responsive pain in cancer."

- “Cancer pain in general responds in a predictable way to analgesic drugs and drug therapy is the mainstay of treatment, successfully controlling pain in 70-90% of patients.”

- Non responsive
  - pain associated with nerve damage
  - 'incident' (movement-related) bone pain.
  - bladder and rectal tenesmus
  - pancreatic pain
  - pain associated with decubitus ulcers or other superficial ulcers

Hanks, G. W. (1991). Br Med Bull **47**(3): 718-31.

Unresponsiveness paradigm

- response of patients to opioid drugs may be influenced by properties inherent in the pain or pain syndrome (such as its pathophysiology)
- ➔ certain types of pain, e.g., neuropathic pains may be unresponsive to these drugs

- Implication
  - Use of opioids is futile and counterproductive

The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions

Portenoy RK, Foley KM, Inturrisi CE.

Pain 1990;43(3):273-86.

Portenoy Foley Inturissi Hyposthesis

- Based on clinical experience and data derived from pharmakokinetic/pharmacodynamic opioid infusion studies in patients with neuropathic cancer pain

Portenoy Foley Inturissi Hypothesis

Definition of Opioid Responsiveness

- the degree of analgesia achieved during dose escalation to either intolerable side effects or the occurrence of 'complete' or 'adequate' analgesia

Portenoy Foley Inturissi Hypothesis

Characteristics of responsiveness

1. opioid responsiveness is a continuum, rather than a quantal phenomenon

2. opioid responsiveness is determined by a diverse group of patient characteristics and pain-related factors, as well as drug-selective effects

Portenoy Foley Inturissi Hyposthesis

Regarding Neuropathic pain

- neuropathic mechanism may reduce opioid responsiveness, but does not result in an inherent resistance to these drugs.

Portenoy Foley Inturissi Hypothesis

Implications for practice

1. Given the complexity of factors contributing to opioid responsiveness and the observation that outcome cannot be reliably predicted, opioids should not be withheld on the assumption that pain mechanism, or any other factor, precludes a favorable response.
2. The clinical use of opioids should include dose escalation to maximally tolerated levels and repeated monitoring of analgesia and other effects.

Since 1990

- Subsequent research extensively validated the Potenoy/Foley/Inturissi hypothesis

Neuropathic pain

Opioids for Neuropathic Pain

2 meta-analyses

1. Tramadol in neuropathic pain
2. Opioids in Neuropathic pain

Tramadol for neuropathic pain

- 5 eligible trials
  - 3 vs placebo
  - 1 vs clomipramine
  - 1 vs morphine.
- 3 placebo trials
  - significant reduction in neuropathic pain
- NNT > 50% pain relief was 3.5 (95% CI 2.4 - 5.9).
- NNH 7.7 (95% CI 4.6 - 20).

Duhmke RM, Cornblath DD, Hollingshead JR. Tramadol for neuropathic pain. Cochrane Database Syst Rev 2004(2):CD003726.

Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials.

Eisenberg E, McNicol ED, Carr DB.

JAMA 2005;293(24):3043-52.

Intermediate-term Studies

- 8 trials provided data on 403 opioid- treated patients

- number of patients per treatment group ranged from 12 to 82
- duration of treatment varied from 8 days to 8 weeks (median, 28 days).

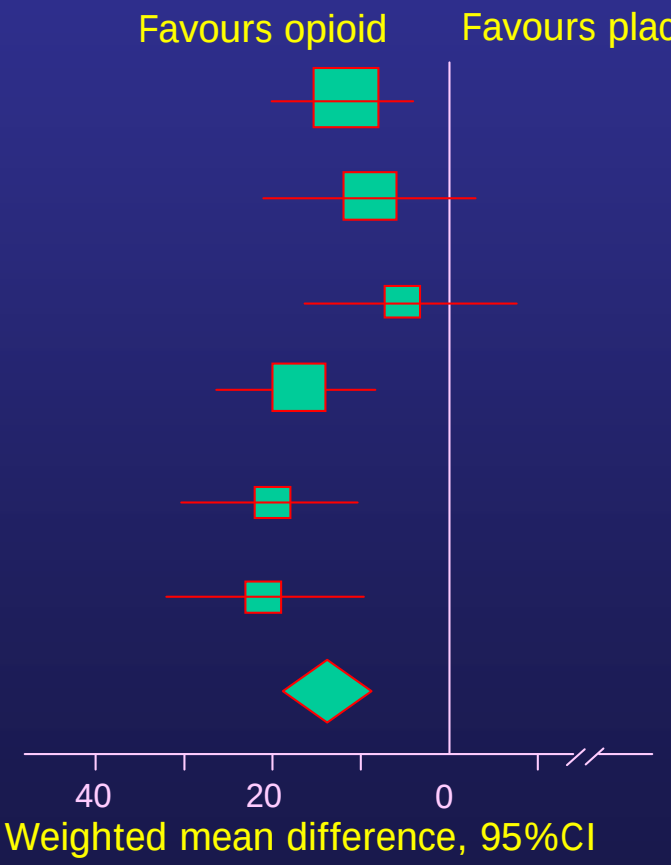
Intermediate duration study results

- All trials positive
- 6/8 studies provided data suitable for pooling
- The meta-analysis included 263 opioid- and 258 placebo-treated patients
- Mean pain intensity to be 14 points lower in opioid-treated patients than in those treated with placebo (95% CI, −18 to −10; *P*_.001)

Efficacy of Opioids in NPs
Meta-analysis of Intermediate Term Studies

(Eisenberg et al, JAMA, 2005)

Author/ Year	Drug	Diagnosis	No of pts in Tx arm: Opioid	No of pts in Tx arm: Placebo
Gimbel 2003	OXY	DPN	82	77
Huse 2001	MO	PLP	12	12
Morley 2003	Meth	Misc	19	19
Raja 2002	MO	PHN	76	76
Watson 1998	OXY	PHN	38	36
Watson 2003	OXY	DPN	36	36
TOTAL			263	258



DPN, painful diabetic polyneuropathy,
PLP, phantom limb pain

PHN, postherpetic neuralgia
Misc, diverse aetiologies

Dose-dependent analgesic

Demonstrated in 2 studies

1. Low and high doses of methadone were each compared separately with placebo, and the higher dose produced a larger effect than the lower dose.

2. In the other study,a direct comparison showed that a high dose of levorphanol produced a significantly larger analgesic effect than the lower dose.

Safety of Opioids in NPs
Meta-analysis of Intermediate Term Studies

(Eisenberg et al, JAMA, 2005)

Numbers-Needed-To-Harm

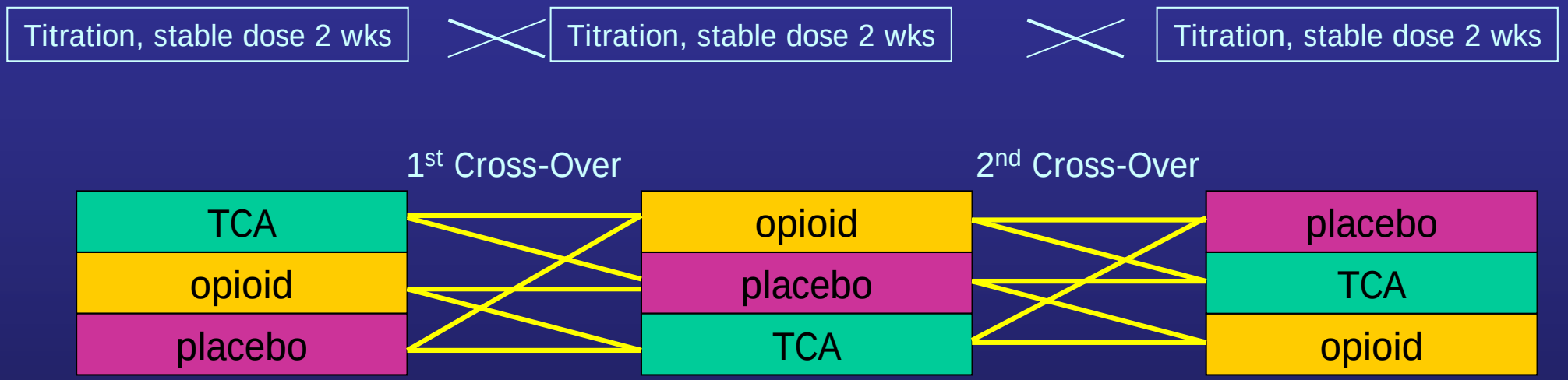
	NNH (95% CI)
Nausea	3.6 (2.9-4.8)
Constipation	4.6 (3.4-7.1)
Drowsiness	5.3 (3.7-8.3)
Vomiting	6.2 (4.6-11.1)
Dizziness	6.7 (4.8-10.0)

Dropouts

- 4 trials provided combinable information regarding the number of dropouts due to adverse events

Opioid	Placebo
13.5%	7.6%

Opioids vs. TCA vs placebo in PHN
Multiple Cross-Over RCT



FLEXIBLE DOSING: TITRATED TO EFFECT

TCA, nortriptyline up to max. 160 mg/d or desipramine,
Opioid, morphine sulphate up to max 240mg/d or methadone

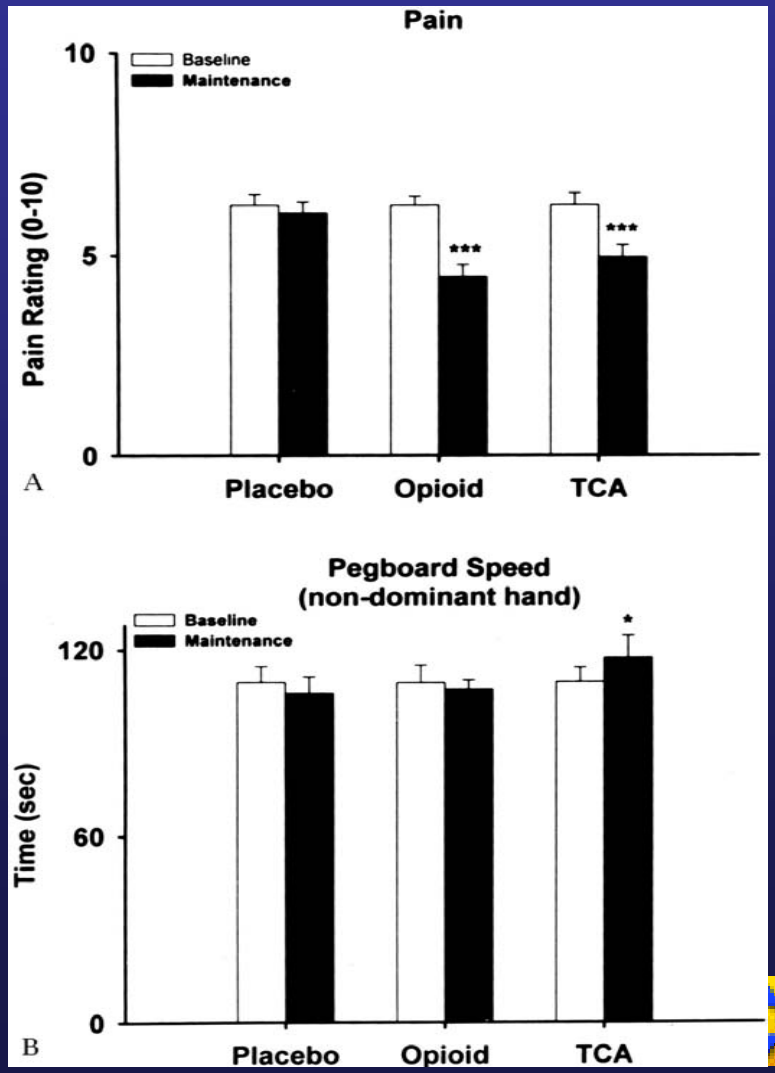
Raja et al 2002

Opioids vs. TCA vs placebo in PHN
Multiple Cross-Over RCT

76 patients recruited
44 completed all 3 arms

Pain relief: Opioid versus TCA equal

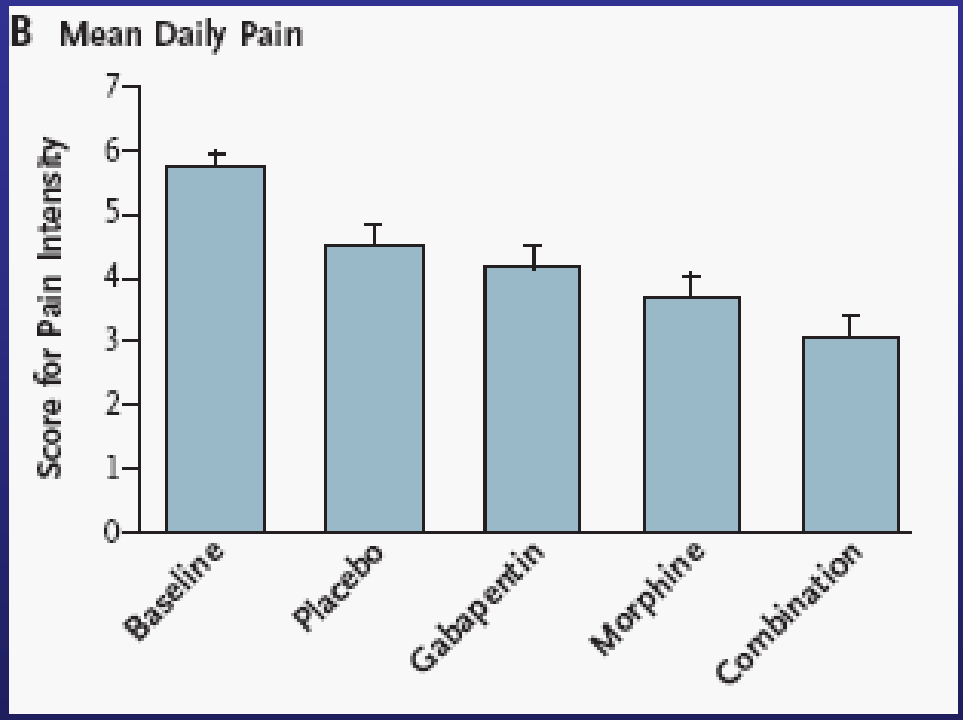
Patient preference for opioid (p 0.06)



Raja et al 2002

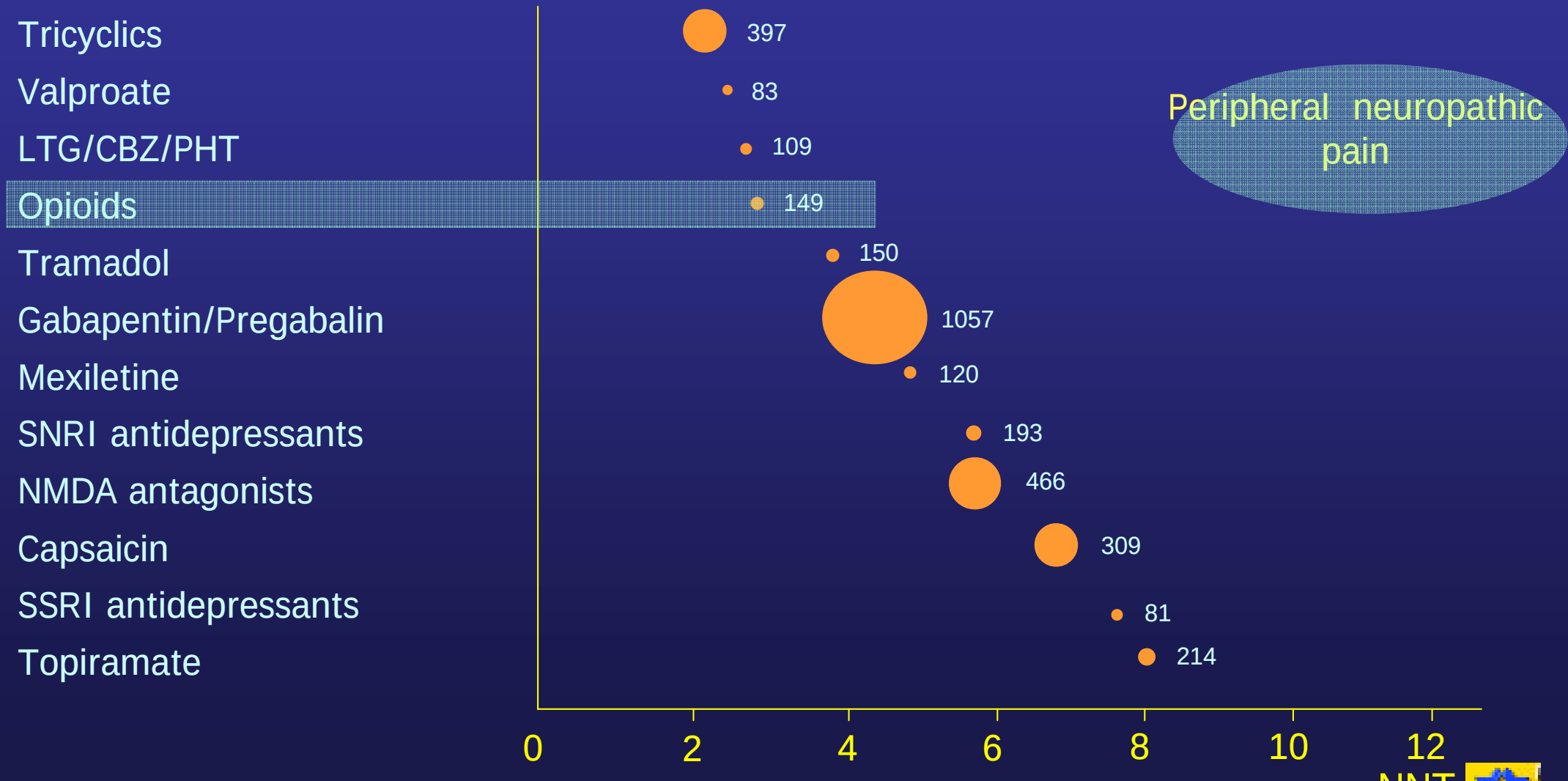
Morphine Vs Gabapentin vs Combination vs Placebo

- double-blind, active placebo-controlled, four-period crossover trial
- 5 week treatment periods
- 41/57 pts completed trial



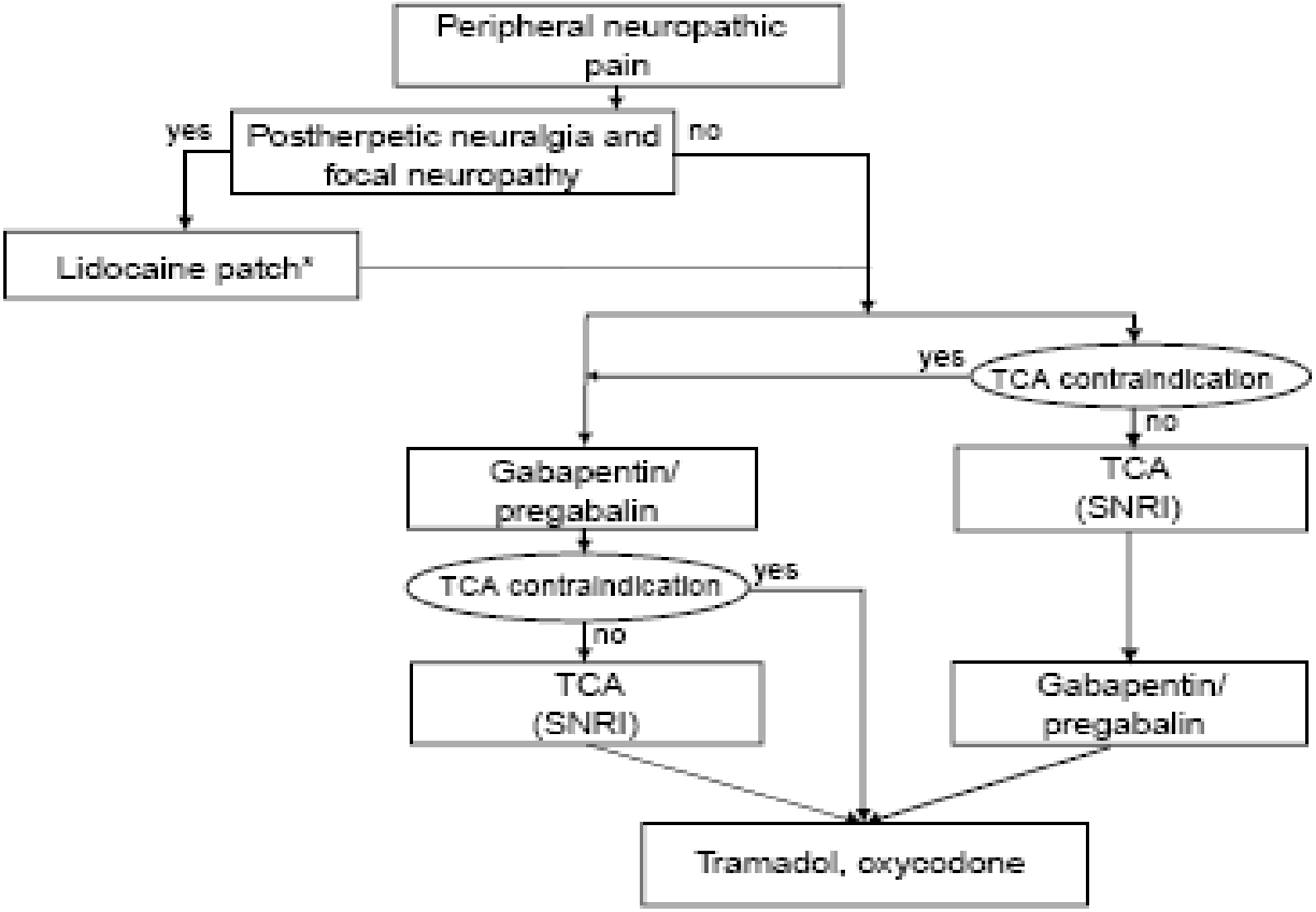
Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005;352(13):1324-34.

NNT map of pharmacotherapy of NP



Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Pain 2005;118(3):289-305.

Algorithm for neuropathic pain treatment: An evidence based proposal



Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Pain 2005;118(3):289-305.

Incident pain pain

Optimization of opioid therapy for preventing incident pain associated with bone metastases.

- Study to determine whether increasing the opioid doses above those sufficient to control pain at rest would reduce the occurrence of these pains.

- 25 consecutive patients with movement-related episodic pain associated with bone metastases,
  - no evident fractures

Mercadante S, Villari P, Ferrera P, Casuccio A.. J Pain Symptom Manage 2004;28(5):505-510.

Optimization of opioid therapy for preventing incident pain associated with bone metastases.

3 phases

1. rapid intravenous titration of the opioid dose to obtain pain relief at rest.

2. opioid doses increased until dose limiting adverse effects

3. opioid dose increases were then stopped, or doses were even reduced, according to patients' satisfaction or development of adverse effects with moderate-severe intensity.

Mercadante S, Villari P, Ferrera P, Casuccio A.. J Pain Symptom Manage 2004;28(5):505-510.

Optimization of opioid therapy for preventing incident pain associated with bone metastases.

- Measures
  - Basal pain intensity and pain induced by movement: NRS 0-10.
  - Opioid-related symptoms
  - total daily doses of oral morphine and other symptomatic drugs were also recorded at daily intervals, and at time of discharge, when the best balance was presumed to be reached.

Mercadante S, Villari P, Ferrera P, Casuccio A.. J Pain Symptom Manage 2004;28(5):505-510.

Optimization of opioid therapy for preventing incident pain associated with bone metastases.

Results

- Basal pain control was achieved after rapid intravenous titration.
- The day after, pain induced by movement significantly improved using mean doses of oral morphine equivalents of 102 mg.
- In the following days, the subsequent increase in opioid doses prescribed despite optimal basal pain control allowed an acceptable level of incident pain intensity until patients' discharge.

Mercadante S, Villari P, Ferrera P, Casuccio A.. J Pain Symptom Manage 2004;28(5):505-510.

Optimization of opioid therapy for preventing incident pain associated with bone metastases.

Adverse effects

- A minority of patients developed adverse effects with an intensity of 2-3 on the scale, requiring symptomatic treatment or decreases in opioid doses.

Mercadante S, Villari P, Ferrera P, Casuccio A.. J Pain Symptom Manage 2004;28(5):505-510.

Conclusions

- A priori determination of pain as opioid resistant is inappropriate
- Opioid responsiveness is a variable that is determined retrospectively after trials of opioid therapy
- It is determined by the degree of relief achieved after opioid titration to maximal effect or maximal tolerated dose
- Since there are intra-individual variability in response to different opioids, in the setting of dose limiting adverse effects, opioid rotation should be considered
- When opioid responsiveness is limited, other analgesic options need to be strongly considered.