Improving assay sensitivity in Phase 3 trials: existing data and future directions

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"Yesterday's home runs don't win today's games."

— Babe Ruth

Gabapentin for the Symptomatic Treatment of Painful Neuropathy in Patients With Diabetes Mellitus

A Randomized Controlled Trial

Miroslav Backonja, MD; Ahmad Beydoun, MD; Keith R. Edwards, MD; Sherwyn L. Schwartz, MD; Vivian Fonseca, MD; Marykay Hes, BS; Linda LaMoreaux, MPH; Elizabeth Garofalo, MD; for the Gabapentin Diabetic Neuropathy Study Group

JAMA, December 1998

Gabapentin for the Treatment of Postherpetic Neuralgia

A Randomized Controlled Trial

Michael Rowbotham, MD; Norman Harden, MD; Brett Stacey, MD; Paula Bernstein, MS; Leslie Magnus-Miller, MD; for the Gabapentin Postherpetic Neuralgia Study Group

Pregabalin for painful HIV neuropathy

A randomized, double-blind, placebo-controlled trial

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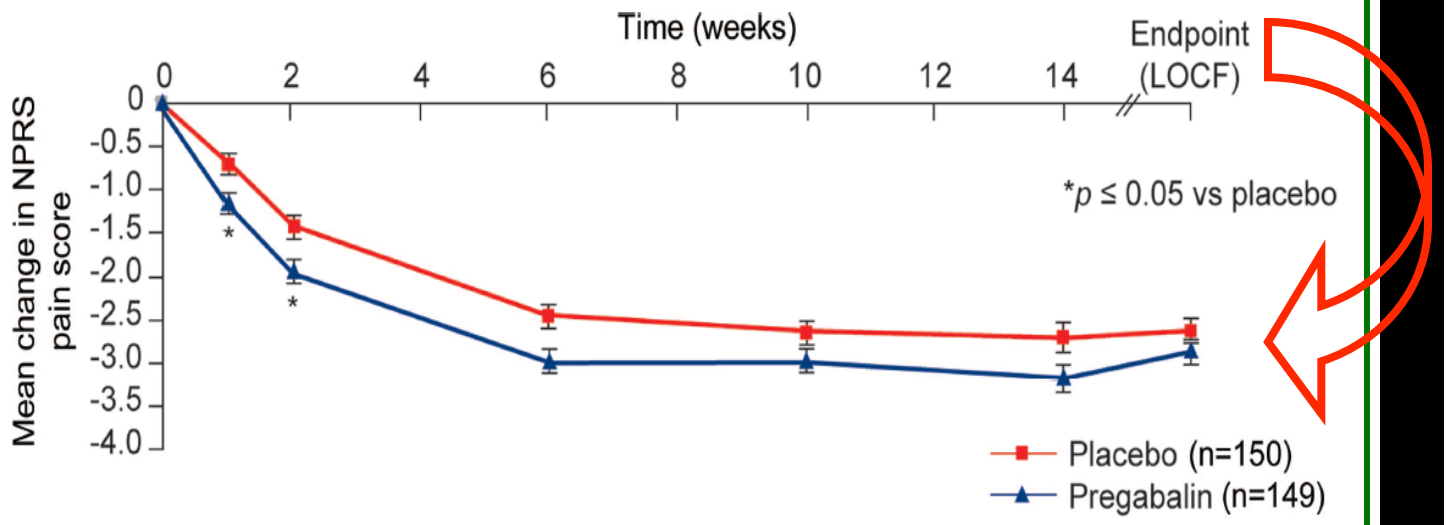
ABSTRACT

Objective: Pregabalin is effective in several neuropathic pain syndromes. This trial evaluated its efficacy, safety, and tolerability for treatment of painful HIV-associated neuropathy.

Figure 3 Mean change from baseline in Numeric Pain Rating Scale score



Conclusions: Pregabalin was well-tolerated, but not superior to placebo in the treatment of painful HIV neuropathy. Factors predicting analgesic response in HIV neuropathy warrant additional research.

Classification of Evidence: This Class II trial showed that pregabalin is not more effective than placebo in treatment of painful HIV neuropathy. *Neurology*® 2010;74:413–420

16 additional recent "negative" neuropathic pain trials (and there are many others)

Bicifadine in painful DPN

Gabapentin enacarbil in painful DPN

Lacosamide in painful DPN (2 trials)

Lamotrigine in painful DPN (2 trials)

Lamotrigine in mixed neuropathic pain conditions

Levetiracetam in postherpetic neuralgia

Oxcarbazepine in painful DPN (2 trials)

Oxcarbazepine in lumbosacral radiculopathy

Pregabalin in painful DPN

Pregabalin in lumbosacral radiculopathy

Topiramate in painful DPN (3 trials)

For most of these results, we do not know which are examples of “drug failure” —

perhaps some of these drugs are not efficacious in the specific neuropathic pain conditions in which they were studied

and which are examples of “study failure” —

some are likely to be failed studies of truly efficacious drugs

for example, pregabalin in painful DPN

“Insanity: doing the same thing over and over again and expecting different results.”

— Albert Einstein

Why have so many recent Phase 3 trials been negative?

1. Preclinical animal models and methods are identifying some drugs that have no or limited efficacy.
2. Phase 2 trials are identifying some drugs that have no or limited efficacy.
3. These recent studies are really "failed" trials.
   - ~ 50% of Phase 3 antidepressant trials of drugs approved for major depression fail...
4. The response in the placebo group was too great.

9. The optimal pain conditions or patients were not studied.
10. Temporal changes in study patients and in study sites may have occurred, for example:
    - patients may be more refractory or have less severe disorder
    - sites have greater financial incentives and recruit much more aggressively.

Some recent findings on placebo effects in neuropathic pain clinical trials

1. **Negative trials show greater improvement in the placebo groups**
   - Katz J, Finnerup NB, Dworkin RH. Clinical trial outcome in neuropathic pain: relationship to study characteristics. Neurology, 2008;70:263-272.

2. **Placebo group response appears to be greater the longer the trial (painful DPN)**
   - Quessy SN, Rowbotham MC. Placebo response in neuropathic pain trials. Pain, 2008;138:479-483.

3. **Placebo group response, but not active treatment group response, is significantly greater in painful DPN compared with PHN trials.**
   - Dworkin RH. Turk DC, Peirce-Sandner S, McDermott MP, Farrar JT, Hertz S, Katz NP, Raja SN, Rappaport BA. Placebo and treatment group responses in postherpetic neuralgia vs. painful diabetic peripheral neuropathy clinical trials in the REPORT database. Pain, 2010;150:12-16.

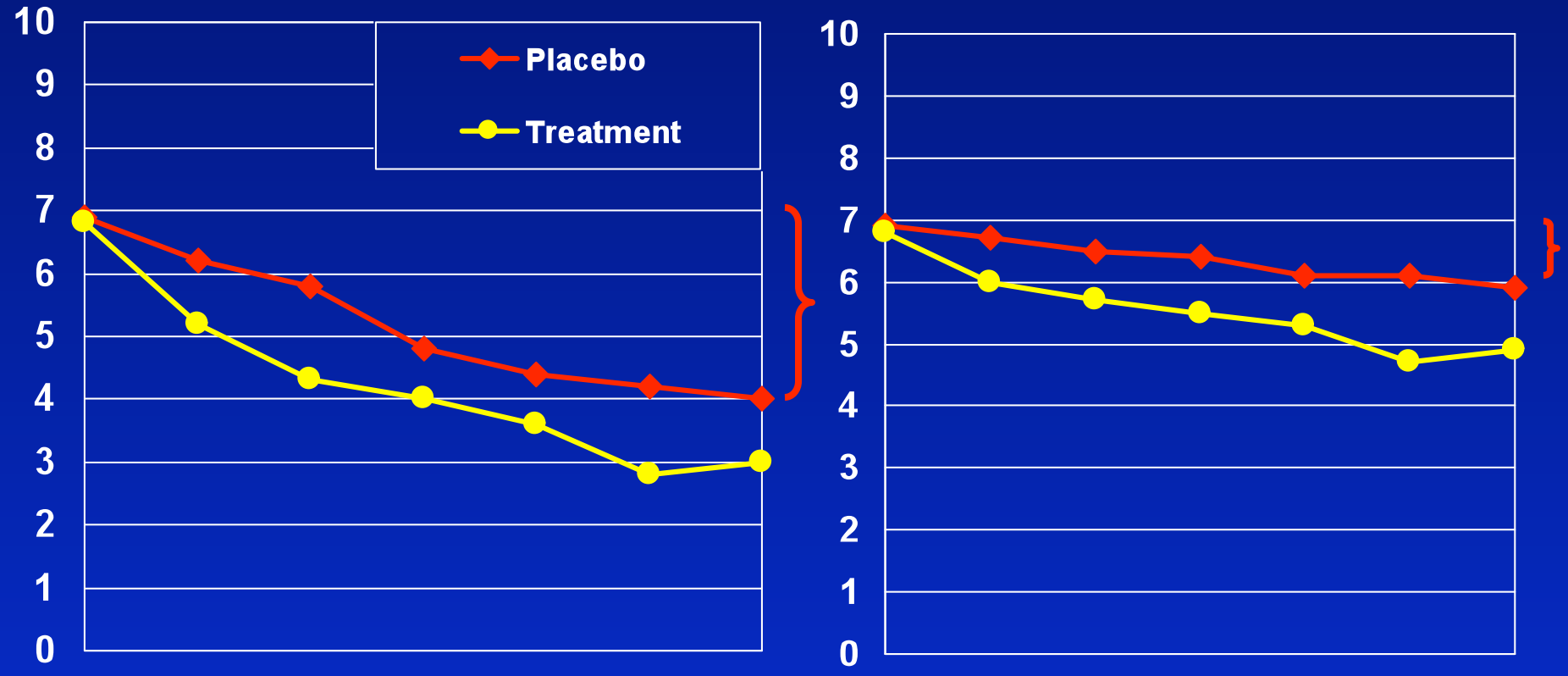
1. Understand relationships between study methodological features and assay sensitivity.
    - perhaps especially placebo group improvement

2. Modify study methodological features to increase assay sensitivity.
    - include efforts to reduce placebo group improvement (?)

What approaches can be used to optimize the design of Phase 3 trials?

- little evidence is available on which to base modifications of existing approaches
- so, any modifications
    1. should be unlikely to *decrease* assay
    2. will ideally increase assay sensitivity
    3. at worst, should have no effect

Reducing placebo group responses may not necessarily increase assay sensitivity



"Standard" approach

"Novel" approach

Patient factors that may be associated with increased assay sensitivity (or reduced placebo group responses)

- **Greater baseline pain severity (≥ 4/10)**
- **Longer duration of pain (i.e., ≥ 6 months)**
- **Lacking history of multiple treatment failures**
- **Clinic referrals vs. advertisements**
- ***Can we do more with the baseline pain diaries?***
- ***Less psychopathology***
- ***Manage patient expectations of improvement***
- **Improve validity of patient ratings with greater training**

Can we do more with baseline pain diaries?

1. **Compliance**
   - e.g., has been ≥ 4/7 baseline pain diaries required
   - why not ≥ 6/7?
2. **Mean pain intensity**
   - typically, mean ≥ 4/10 for baseline required (also, 3 or 5)
   - sometimes maximums: 9/10 (high-concentration capsaicin), 75-90/100 (several OA trials, memantine)
   - should we consider maximum of 8, 8.5, or 9/10?
3. **Variability and extreme ratings, *for example***
   - include if ≤ 25% variability (oxcarbazepine,zonisamide)
   - include if ≥ 4/7 ratings ≥ 4/10 (oxcarbazepine,pregabalin)
   - exclude if any baseline 10s or any baseline 0s?
   - e.g., exclude if > 3 baseline 9s or > 3 baseline 1s?
4. **Consistency**
   - e.g., exclude if all baseline daily ratings are identical?

"Individuals with a greater PVI (pain variability index) at baseline were more likely to be responders; this effect was seen almost exclusively in those randomized to placebo as compared to those receiving milnacipran, suggesting that a high pain variability may be a predictor of a placebo response."

Harris RE, et al. Characterization and consequences of pain variability in individuals with fibromyalgia. Arthritis Rheum 2005;52:3670-3674.

"Thus, patients with high variability within each MLN (milnacipran) treatment arm had the highest pain responder rates, but the lowest relative responder rates compared with placebo…High pain variability may differentially add error variance to outcomes in clinical trials, lowering the power to detect a treatment effect."

Palmer RH, Turk DC, Hufford MR, Wang Y. The impact of pain variability on response to milnacipran and placebo in two trials of patients with fibromyalgia (FM). To be presented at the 13th World Congress on Pain, Montreal, August 2010.

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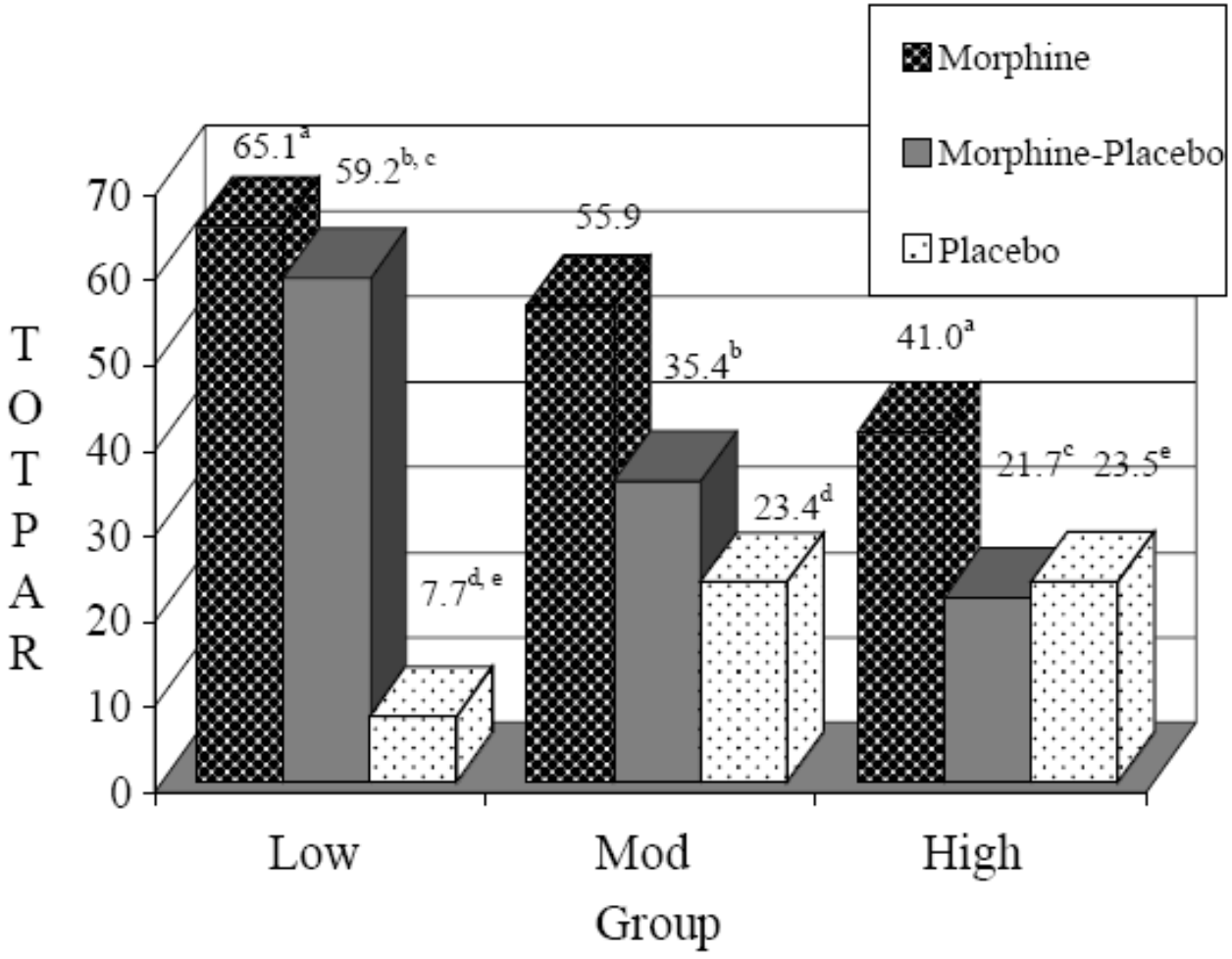

a-e=significant pairwise comparisons

a=.026 b=.015 c=.0001 d=.03 e=.03

Fig. 2. TOTPAR results.

"...Though it is natural to hope for a positive outcome during the trial, we want you to be aware that there is a good likelihood that you are on placebo during this trial. Though you are likely to appreciate the care that you get from the study staff in this trial, it is very important that you don't tell us that you are better if you're really not, just because you are appreciative of the study staff, and you feel that you will be letting them down if you don't improve. We need you to report your condition as accurately as you possibly can..."

—D.L. Zimbroff, 2001

Patient phenotypes?

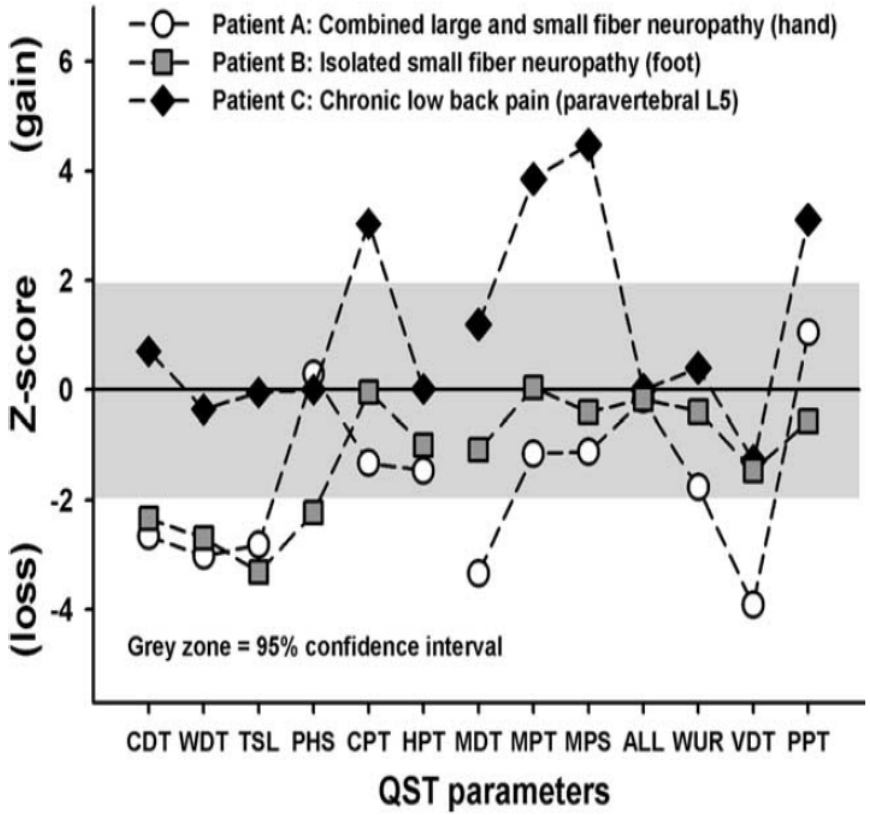

Fig. 4. *Z*-score QST profiles of selected patients. *Patient A* (open circles) presents the QST profile of a 64-year-old man suffering from vibration induced vasospastic syndrome with an intermittent Raynaud-syndrome and painless dysaesthesia of the right hand after working with a chain-saw for more than 20 years. The profile shows a combined loss of sensory function for small fiber mediated stimuli (note the thermal detection thresholds (CDT, WDT, TSL)), and for large fiber mediated stimuli (note the mechanical detection threshold for von Frey-filaments (MDT), and the vibration detection threshold (VDT) outside the 95% confidence interval of the normal standard distribution of healthy subjects = grey zone). *Patient B* (filled squares) shows the QST profile of a 60-year-old woman with stocking distributed burning pain over feet for more than 1 year. Main pain was 50 on a 0–100 numerical rating scale. The QST profile confirms a small fiber sensory neuropathy (note the cold (CDT), warm detection thresholds (WDT), thermal sensory limen (TSL), and numbers of paradoxical heat sensations (PHS) outside the normal range as presented by the grey zone). *Patient C* (filled triangles) shows the QST profile of a 45-year-old woman with chronic low back pain attributed to facet joint arthropathy. The QST profile presents positive sensory signs reflected by a gain of function for the mechanical pain sensitivity to sharp (MPT and MPS), blunt stimuli (PPT), and for cold pain (CPT).

Investigator factors that may be associated with increased assay sensitivity

1. Greater experience and training for study staff
2. Fewer and more structured contacts between study staff and patients
    - but would this increase the number of patients withdrawing from the trial?
3. To the greatest extent possible, blind investigators and study staff to the protocol.
4. Reduce financial incentives and other methods used to accelerate enrollment

Research design factors

1. Duration of trial: as short as possible (but would a 2-week baseline provide a better patient assessment?)
2. Fewer treatment arms
3. Flexible vs. fixed dosage designs
4. Role of concomitant analgesics
5. Better reliability, validity, and, especially, *responsiveness* of outcome measures
6. Composite (vs. unidimensional) outcome measures, for example, OMERACT-OARSI responder index
7. More attention is needed to actual methods of administration of the outcome measures

15. Geographic region (e.g., North America and Western Europe vs. elsewhere?)

Can Phase 3 trials continue to exclude patients who are taking other analgesics?

Concomitant analgesics are typically not permitted, except for rescue acetaminophen/paracetamol.

It is argued that evaluations of an investigational agent in patients already receiving analgesic treatment will be less likely to demonstrate efficacy.

But, patients who either

(1) are not taking any of the available analgesic medications, or
(2) can be easily withdrawn from such medications

may be relatively refractory and therefore less likely to respond to a new treatment.