NIH Workshop:
Developing Meaningful Endpoints for Pain Clinical Trials
Virtual Workshop

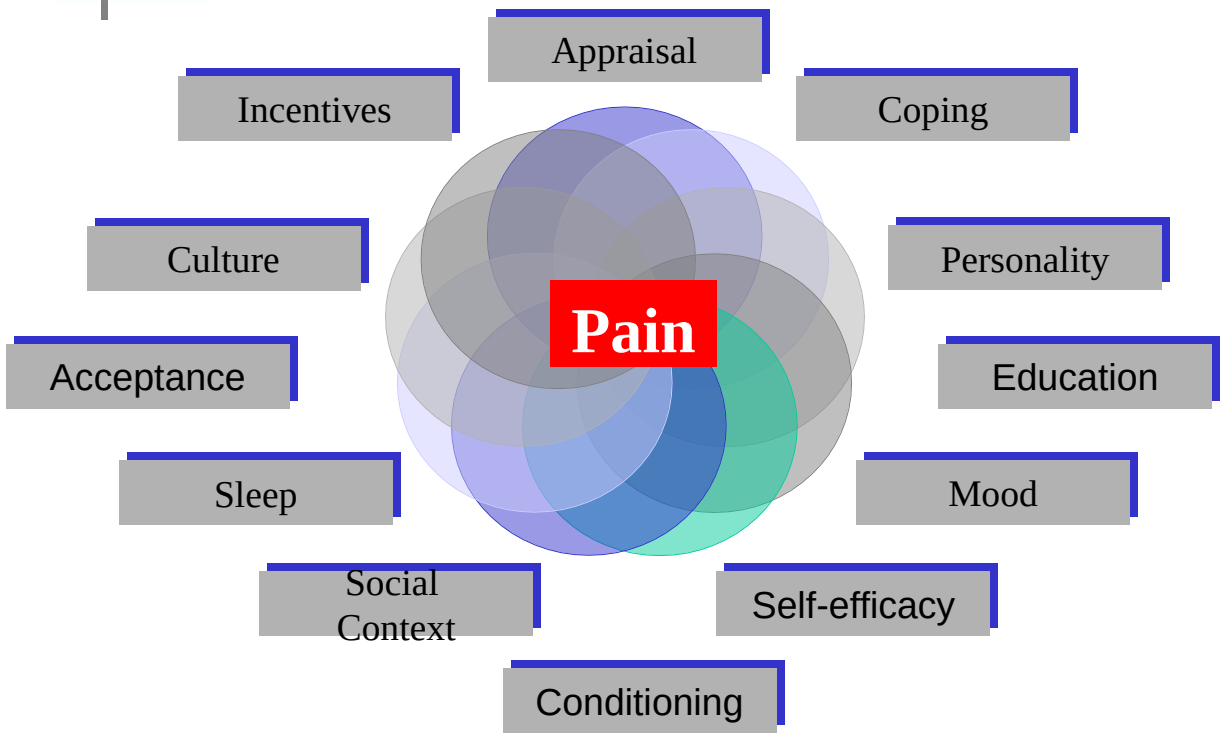
Patient-Reported Outcomes

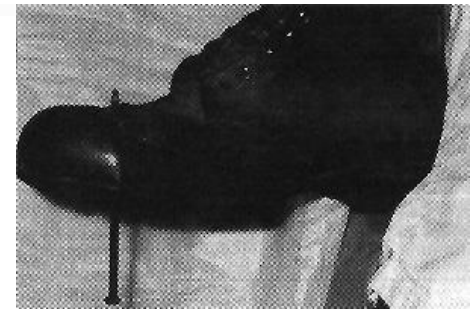
Rob Edwards, Ph.D.
BWH Department of Anesthesiology

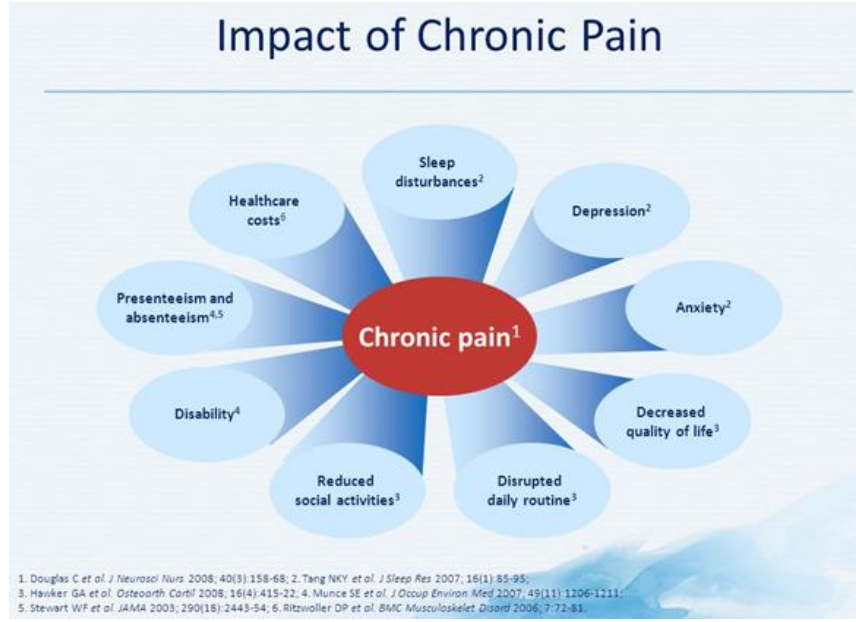
NIH · Helping to End Addiction Long-term

HARVARD MEDICAL SCHOOL
BWH BRIGHAM AND WOMEN'S HOSPITAL

Variability in Pain is the Rule Rather than the Exception







Development of Pain Outcome Measures (Largely PROs)

Pain 113 (2005) 9–19

PAIN

www.elsevier.com/locate/pain

Topical Review and Recommendations

Core outcome measures for chronic pain clinical trials: IMMPACT recommendations

Robert H. Dworkin[a,*], Dennis C. Turk[b], John T. Farrar[c], Jennifer A. Haythornthwaite[d], Mark P. Jensen[b], Nathaniel P. Katz[e], Robert D. Kerns[f], Gerold Stucki[g], Robert R. Allen[h], Nicholas Bellamy[i], Daniel B. Carr[j], Julie Chandler[k], Penney Cowan[l], Raymond Dionne[m], Bradley S. Galer[n], Sharon Hertz[o], Alejandro R. Jadad[p], Lynn D. Kramer[q], Donald C. Manning[r], Susan Martin[s], Cynthia G. McCormick[t], Michael P. McDermott[u], Patrick McGrath[v], Steve Quessy[w], Bob A. Rappaport[o], Wendye Robbins[x], James P. Robinson[b], Margaret Rothman[y], Mike A. Royal[z], Lee Simon[o], Joseph W. Stauffer[aa], Wendy Stein[ab], Jane Tollett[ac], Joachim Wernicke[ad], James Witter[o]

Pain 125 (2006) 208–215

PAIN

www.elsevier.com/locate/pain

Review and recommendations

Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations

Dennis C. Turk [a,*], Robert H. Dworkin [b], Laurie B. Burke [c], Richard Gershon [d], Margaret Rothman [e], Jane Scott [c], Robert R. Allen [f,1], J. Hampton Atkinson [g], Julie Chandler [h], Charles Cleeland [i], Penny Cowan [j], Rozalina Dimitrova [k], Raymond Dionne [1,2], John T. Farrar [m], Jennifer A. Haythornthwaite [n], Sharon Hertz [c], Alejandro R. Jadad [o], Mark P. Jensen [a], David Kellstein [p,3], Robert D. Kerns [q,r], Donald C. Manning [s], Susan Martin [t], Mitchell B. Max [1,2], Michael P. McDermott [b], Patrick McGrath [u], Dwight E. Moulin [v], Turo Nurmikko [w], Steve Quessy [x], Srinivasa Raja [n], Bob A. Rappaport [c], Christine Rauschkolb [y,4], James P. Robinson [a], Mike A. Royal [z,5], Lee Simon [aa], Joseph W. Stauffer [ab,6], Gerold Stucki [ac], Jane Tollett [ad], Thorsten von Stein [ac,7], Mark S. Wallace [g], Joachim Wernicke [af], Richard E. White [ag], Amanda C. Williams [ah], James Witter [c], Kathleen W. Wyrwich [ai]

Among the criteria used in evaluating potential core outcome measures were: (1) appropriateness of the measure's content and conceptual model; (2) reliability; (3) validity; (4) responsiveness; (5) interpretability; (6) precision of scores; (7) respondent and administrator acceptability; (8) respondent and administrator burden and feasibility; (9) availability and equivalence of alternate forms and methods of administration (e.g. self-report, interviewer); and (10) availability and equivalence of versions for different cultures and languages

Table 1
Recommended process for developing outcome measures for pain clinical trials[a]

- I. Identify scientific approach
  - A. Overall question
  - B. Conceptual model or theoretical approach
  - C. Scope of assessment
- II. Establish
  - A. Target population
  - B. Factors or concepts to be included
    1. Specific goal of outcome measure
    2. Specific traits
    3. Need for independent or overlapping subscales
- III. Develop item pool
  - A. Methods
    1. Literature review
    2. Focus groups with patients and experts
    3. In-depth interviews with patients and experts
  - B. Determine format
    1. Individual items
    2. Scale properties
  - C. Consider methods of
    1. Data collection
    2. Scoring
    3. Analysis
- IV. Item evaluation
  - A. Components
    1. Minimize patient burden
    2. Evaluate language and cross-cultural equivalence
    3. Test in target population (cognitive interviewing or debriefing)
    4. Revise and repeat as necessary to finalize format and item wording
    5. Develop scoring algorithm
  - B. Measurement approach
    1. Classical test theory
    2. Item response theory
  - C. Field test items
    1. Collect response data for items from target population
    2. Assess dimensionality of items
    3. Locate "gaps" in the construct assessment
- V. Instrument evaluation – evaluate psychometric properties in target populations
  - A. Reliability
  - B. Validity
  - C. Responsiveness
- VI. Complete instrument development
  - A. Revise instrument if necessary
  - B. Finalize instrument
  - C. Develop user manual and instructions to respondents

[a] Although the recommended sequence is presented as if it were a linear process, the development of measures is frequently an iterative process.

Patient Perspective

Pain 137 (2008) 276–285

PAIN

www.elsevier.com/locate/pain

Identifying important outcome domains for chronic pain clinical trials: An IMMPACT survey of people with pain

Dennis C. Turk [a,*], Robert H. Dworkin [b], Dennis Revicki [c], Gale Harding [c], Laurie B. Burke [d], David Cella [e], Charles S. Cleeland [f], Penney Cowan [g], John T. Farrar [h], Sharon Hertz [d], Mitchell B. Max [i], Bob A. Rappaport [d]

IASP

PAIN® 152 (2011) 2283–2286

www.elsevier.com/locate/pain

Comparing patients' and clinician-researchers' outcome choice for psychological treatment of chronic pain

Malcolm Beale [a], Matteo Cella [b,*], Amanda C. de C. Williams [b]

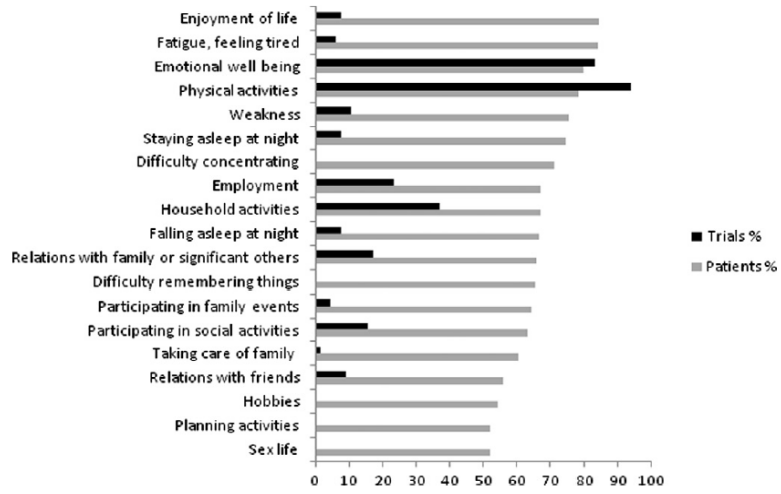


Table 4
Mean importance ratings of patient reported outcomes

Patient outcome area	*N*	Response 8–10 percent	Scale[a] mean (SD)
1. Falling asleep at night	823	66.7	7.8 (2.78)
2. Staying asleep at night	823	74.8	8.3 (2.45)
3. Sex life	823	51.9	6.6 (3.49)
4. Taking care of family such as children, spouses, parents or other relatives	823	60.6	7.1 (3.36)
5. Relations with family, relatives or significant others	823	66.0	7.7 (2.75)
6. Relations with friends	823	55.8	7.2 (2.76)
7. Employment	823	67.2	7.6 (3.25)
8. Household activities (cleaning cooking, running errands)	823	67.0	7.9 (2.36)
9. Planning activities	823	52.2	7.0 (2.87)
10. Participating in family events/ activities	823	64.3	7.7 (2.67)
11. Participating in recreational and social activities	823	63.3	7.7 (2.61)
12. Physical activities (walking, climbing stairs, bending, squatting, lifting)	823	78.1	8.4 (2.33)
13. Hobbies	823	54.4	7.1 (2.86)
14. Enjoyment of life	823	84.4	8.8 (2.05)
15. Emotional well-being (feeling sad, depressed, less motivated)	823	79.6	8.6 (2.27)
16. Fatigue, feeling tired	823	84.0	8.8 (2.01)
17. Weakness	823	75.3	8.3 (2.42)
18. Difficulty concentrating	823	71.3	8.0 (2.62)
19. Difficulty remembering things	823	65.4	7.6 (3.06)

[a] Responses based on a 0–10 scale, where 0 represents "not at all important" and 10 represents "extremely important".

Patient (Not Provider) Ratings

Pain 102 (2003) 289–296

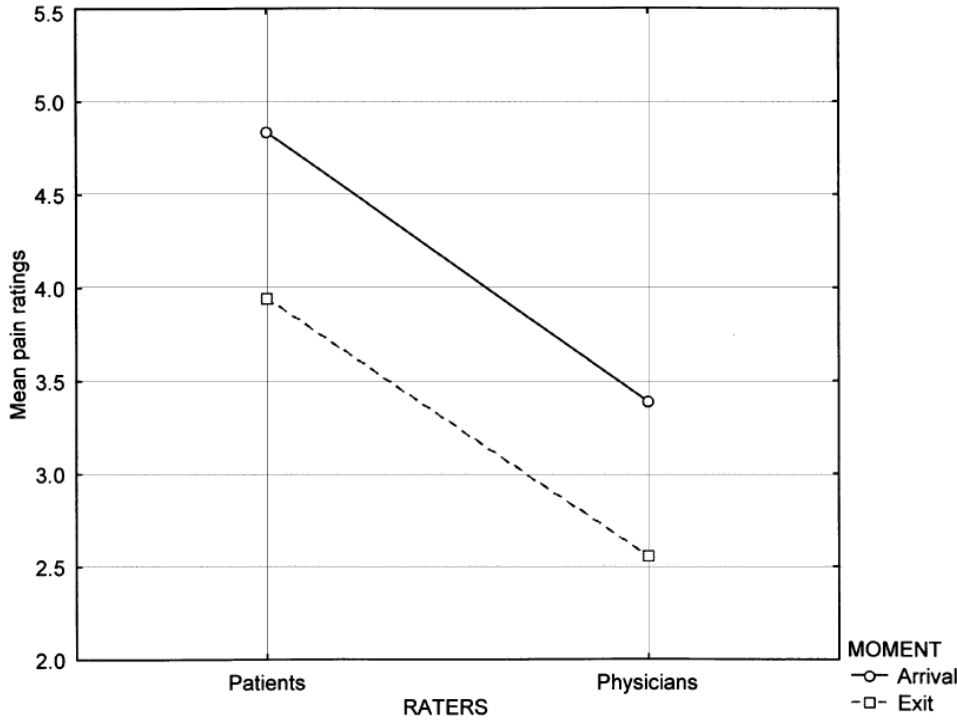
PAIN

www.elsevier.com/locate/pain

Pain rating by patients and physicians: evidence of systematic pain miscalibration

Laetitia Marquié[a,*], Eric Raufaste[a], Dominique Lauque[b], Claudette Mariné[a], Marie Ecoiffier[b], Paul Sorum[c,d]

Providers systematically under-estimate patients' pain, and this effect gets larger with more experience and with a gender difference.



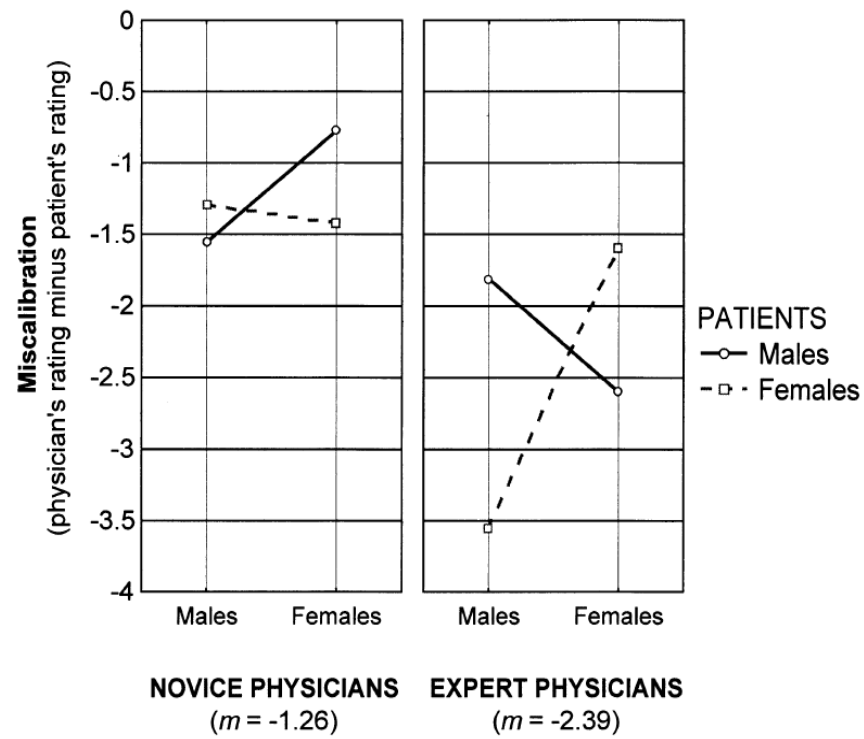


Fig. 1. Comparison of pain ratings by patients and physicians depending on the moment of assessment.

Many Pain Rating Options

With Varying Predictors:

J Pain. 2019 May ; 20(5): 540–556. doi:10.1016/j.jpain.2018.11.004.

Preoperative Psychosocial and Psychophysical Phenotypes as Predictors of Acute Pain Outcomes after Breast Surgery

Kristin L Schreiber[1], Nantthasorn Zinboonyahgoon[2], Xinling Xu[1], Tara Spivey[3], Tari King[3], Laura Dominici[3], Ann Partridge[4], Mehra Golshan[3], Gary Strichartz[1], and Rob R. Edwards[1]

Appendix 1:: Pain impact questions from the Breast Cancer Pain Questionnaire (BCPQ)

Subjects answered the following questions at 2 weeks following surgery via email link to electronic Redcap survey. Pain impact score= sum of ratings on these 14 items Below is a list of statements. Please indicate how you have been feeling during the last month:

1=never 2=to some degree 3=quite a bit 4=very much

I often say no to taking part in leisure activities because of discomfort due to my surgery.

My discomfort affects interactions with friends and family.

My discomfort gets me down

My discomfort after the surgery is a burden for my family and friends

My discomfort after the surgery makes me nervous

My discomfort after the surgery is an unpleasant reminder of my illness

My discomfort after the surgery for breast cancer is the reason I don't do the things I want to do

I sometimes think that pain could be an indication that I still have breast cancer

Discomfort consumes my daily life

My discomfort makes me feel like I am a bad partner

I have difficulty concentrating

I have more difficulty concentrating now than before my surgery for breast cancer

I feel that I don't have the energy to solve problems

I feel that I quickly get mentally fatigued after surgery

Patient Prediction of Pain Intensity

Univariate Association of predictors with moderate-severe pain at 2 weeks after surgery

Patient Characteristics	All	Mild or no pain (BPI ave ≤ 3/10)	Moderate-severe pain (BPI ave >3/10)	P-value
Psychosocial traits				
Catastrophizing (PCS)	4.0 (1.0–8.0)	3.5 (0.0–7.0)	4.0 (1.0–10.3)	0.319
PROMIS Anxiety	17 (13–20)	17 (13–19)	17 (14–20)	0.288
PROMIS Depression	11 (9–14)	11 (9–14)	12 (10–15)	0.011

correlate Prediction of Pain Impact

Univariate Association of predictors with Pain Impact at 2 weeks

Patient Characteristics	Pain Impact, N=216	P-value
Catastrophizing (PCS)	0.34	<0.0001
PROMIS Anxiety	0.44	<0.0001
PROMIS Depression	0.47	<0.0001

Recommendations

Table 1
Recommended core outcome measures for clinical trials of chronic pain treatment efficacy and effectiveness

Pain
11-point (0–10) numerical rating scale of pain intensity
Usage of rescue analgesics
Categorical rating of pain intensity (none, mild, moderate, severe) in circumstances in which numerical ratings may be problematic
Physical functioning (either one of two measures)
Multidimensional Pain Inventory Interference Scale
Brief Pain Inventory interference items
Emotional functioning (at least one of two measures)
Beck Depression Inventory
Profile of Mood States
Participant ratings of global improvement and satisfaction with treatment
Patient Global Impression of Change
Symptoms and adverse events
Passive capture of spontaneously reported adverse events and symptoms and use of open-ended prompts
Participant disposition
Detailed information regarding participant recruitment and progress through the trial, including all information specified in the CONSORT guidelines

Research Paper
PAIN

Reporting of IMMPACT-recommended core outcome domains among trials assessing opioids for chronic non-cancer pain

Sohail M. Mulla[a,b], Amna Maqbool[c], Laxsanaa Sivananthan[c], Luciane C. Lopes[d], Stefan Schandelmaier[e,f], Mostafa Kamaleldin[a], Sandy Hsu[a], John J. Riva[g], Per Olav Vandvik[h], Ludwig Tsoi[i], Tommy Lam[j], Shanil Ebrahim[a,k,l,m], Bradley C. Johnston[m,n,o], Lori Olivieri[p], Luis Montoya[q], Regina Kunz[e], Anne Scheidecker[r], D. Norman Buckley[k,s], Daniel I. Sessler[t], Gordon H. Guyatt[a,u], Jason W. Busse[a,k,s,*]

Table 2
Reporting of IMMPACT-recommended core outcome domains.

Outcome domain	Number of trials (n = 156), n (%)
Pain	154 (98.7)
Symptoms and adverse events	146 (93.6)
Participant disposition	118 (75.6)
Physical functioning	71 (45.5)
Participant ratings of improvement and satisfaction with treatment	67 (42.9)
Sleep and fatigue	49 (31.0)
Emotional functioning	44 (28.2)
Role functioning	29 (18.6)
Interpersonal functioning	11 (7.1)

Pain Intensity

No systematic difference in assay sensitivity between “average” pain and “worst” pain

Table 1
Recommended core outcome measures for clinical trials of chronic pain treatment efficacy and effectiveness

Pain
11-point (0–10) numerical rating scale of pain intensity
Usage of rescue analgesics
Categorical rating of pain intensity (none, mild, moderate, severe) in circumstances in which numerical ratings may be problematic

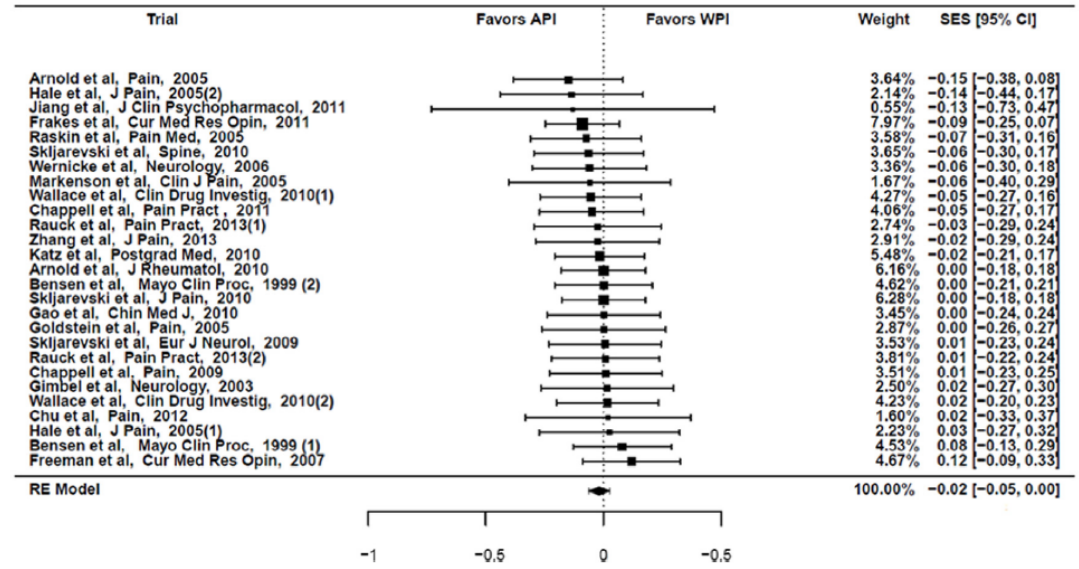
American Pain Society RESEARCH EDUCATION TREATMENT ADVOCACY
PUBLISHED BY ELSEVIER
The Journal of Pain, Vol 19, No 9 (September), 2018: pp 953-960
Available online at www.jpain.org and www.sciencedirect.com

Review Article

A Comparison of the Assay Sensitivity of Average and Worst Pain Intensity in Pharmacologic Trials: An ACTTION Systematic Review and Meta-Analysis

Shannon M. Smith,* Mark P. Jensen,† Hua He,‡ Rachel Kitt,§ James Koch,¶ Andrew Pan,‖ Laurie B. Burke,**,†† John T. Farrar,‡‡,§§,¶¶,‖‖ Michael P. McDermott,***,†††,‡‡‡ Dennis C. Turk,§§§ and Robert H. Dworkin*,‡‡‡,§§§,¶¶¶

An NRS measure of pain intensity in the last day/week (0-10, ‘No pain’ to ‘Pain as bad as you can imagine’) is recommended (over VAS and VRS). In addition, the % of patients obtaining reductions in pain intensity from baseline of at least 30% and at least 50% should be reported.



What Goes Into Ratings?

Best Practice & Research Clinical Rheumatology
Vol. 17, No. 4, pp. 575–592, 2003
doi:10.1016/S1521-6942(03)00031-7, www.elsevier.com/locate/jnlabr/yberh

BEST PRACTICE & RESEARCH

4

Measuring clinical pain in chronic widespread pain: selected methodological issues

Michael Gendreau MD, PhD
Chief Medical Officer
Cypress Bioscience, Inc., 4350 Executive Drive, Suite 325, San Diego, CA 92121, USA

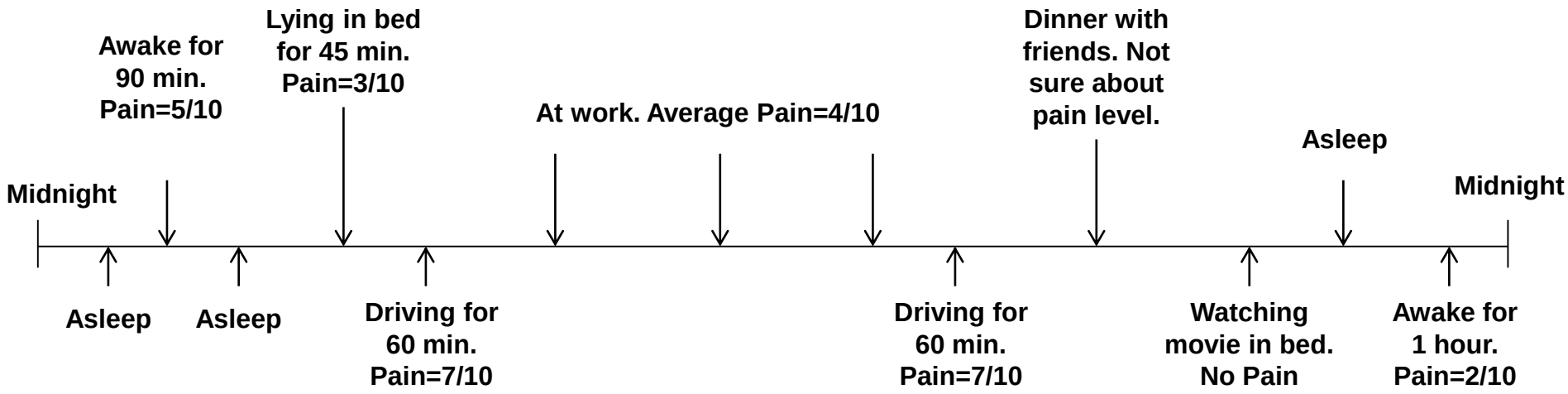
Michael R. Hufford* PhD
Vice President, Scientific Affairs
Invivodata® Inc., 2100 Wharton Street, Suite 505, Pittsburgh, PA 15203, USA

Arthur A. Stone PhD
Professor and Vice Chair
Department of Psychiatry and Behavioural Science, Putnam Hall, Stony Brook University, Stony Brook, NY 11794, USA

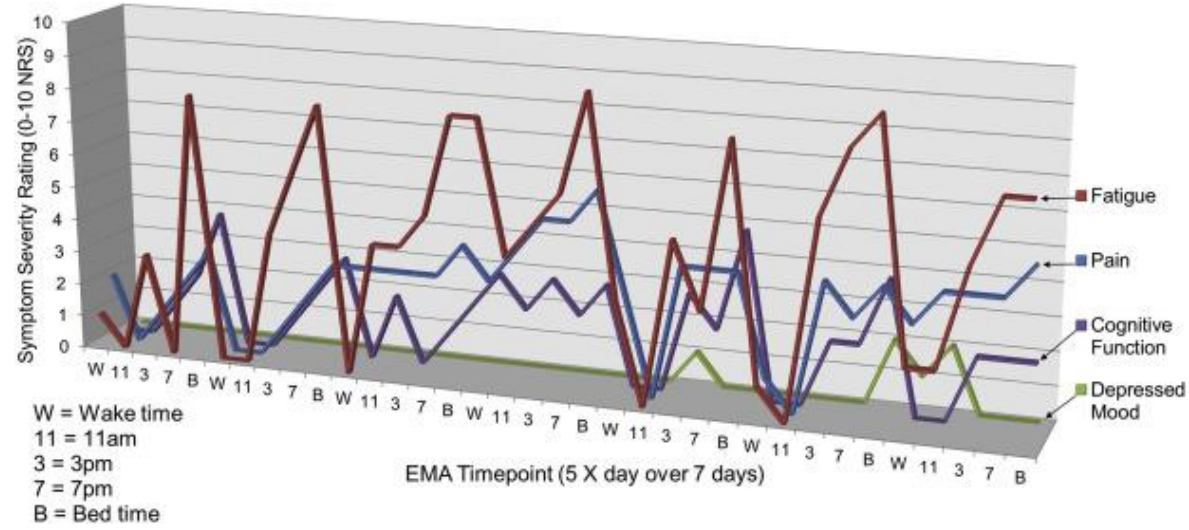
Table 1. Paired *t*-tests: baseline pain methods.

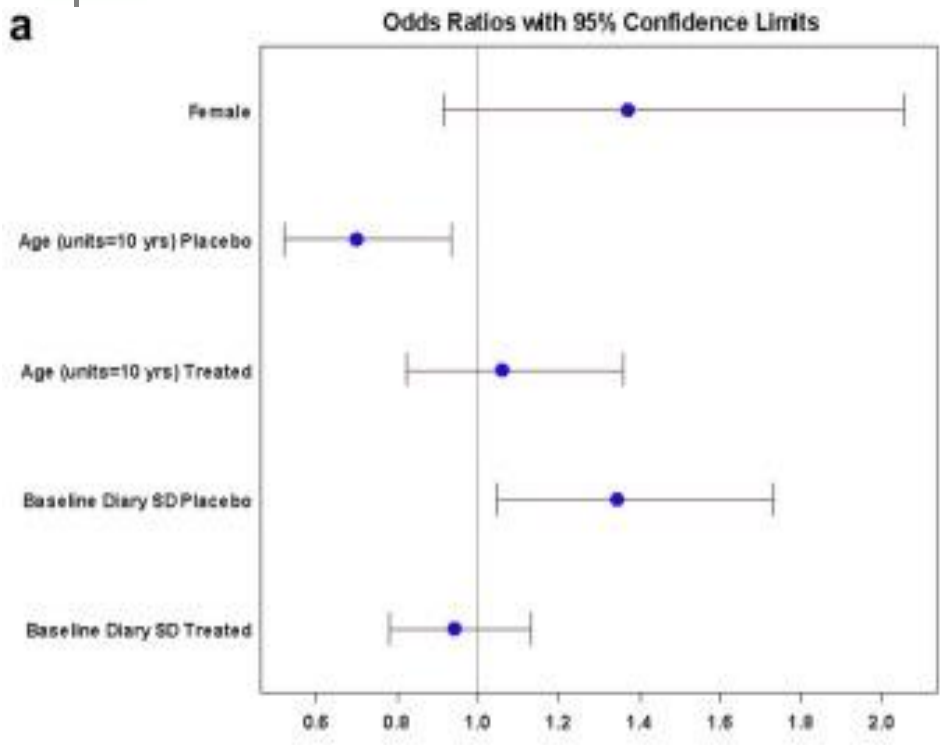
Method	Mean (SD) baseline	Compared with	*t*-test result
PED real-time (EMA)	5.12 (1.3)	PED weekly recall	$t = 2.95(13)$; $P < 0.01$
PED weekly recall	6.0 (1.6)	In-clinic recall	$t = 2.64(12)$; $P < 0.01$
In-clinic recall	7.2 (1.3)	PED real-time (EMA)	$t = 4.67(12)$; $P < 0.01$

There are systematic differences across different modes of pain intensity assessment

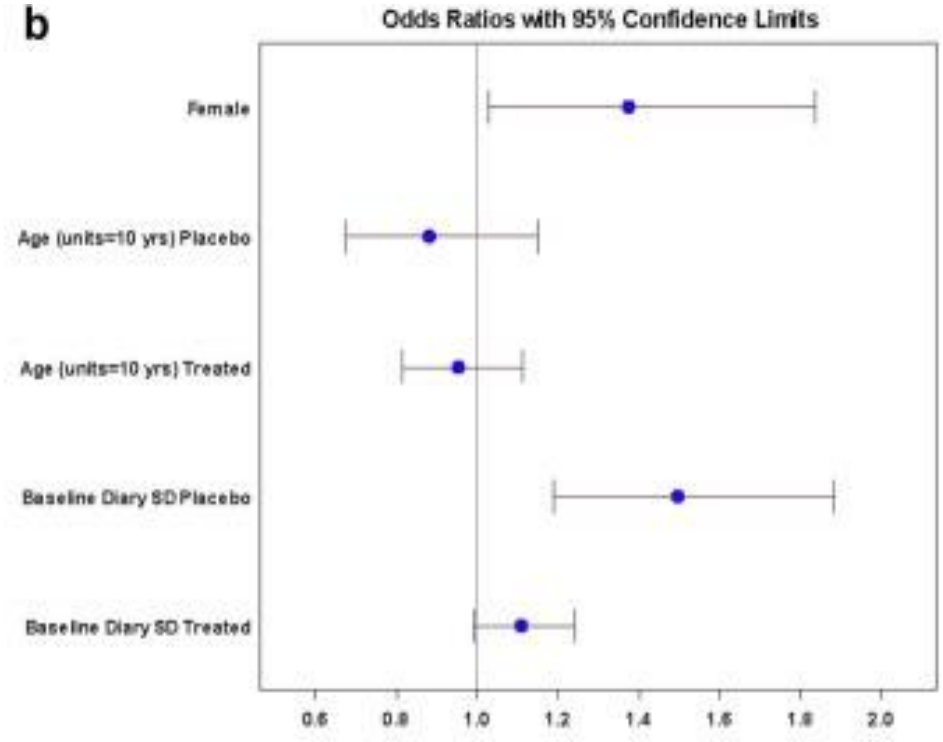


Ecological Momentary Assessment





Baseline Diary SD = Baseline 7 day diary standard deviation in quintile groups.



Baseline Diary SD = Baseline 7 day diary standard deviation in quintile groups.

Evoked Pain

Staircase-evoked Pain May be More Sensitive Than Traditional Pain Assessments in Discriminating Analgesic Effects

A Randomized, Placebo-controlled Trial of Naproxen in Patients With Osteoarthritis of the Knee

Roi Treister, PhD, Erica Suzan, PhD,* Oluwadolapo D. Lawal, MPH,† and Nathaniel P. Katz, MD†‡*

Perhaps the most important implication of our results is the robust reduction in the number of participants needed to demonstrate analgesic efficacy. By using the StEPP EPM rather than the conventional pain-at-rest outcome, one can reduce the recruitment of study participants by 40%. When compared with the WOMAC pain subscale, recruitment can be reduced by 14%. This significant reduction in study participants permits shorter, less complicated (eg, fewer study sites, less variance because of fewer study sites), and more cost-effective trials.

TABLE 4. Results of the Pain-related Measures

	Mean (SD)					
Pain Assessments	Placebo Change	Naproxen Change	Treatment Difference	Treatment Difference (95% CI)	*P*	Cohen *d* SES
Evoked pain	−0.2 (2.4)	−1.2 (2.7)	−1.1 (2.3)	1.7, −0.5	**0.001**	0.47
WOMAC*	−0.9 (3.2)	−2.9 (3.3)	−2.0 (4.6)	−3.2 −0.7	**0.003**	0.43
Pain-at-rest (spontaneous pain)	0.4 (2.2)	−0.3 (2.2)	0.7 (2.0)	−1.3, −0.2	**0.008**	0.36
Pain diary	−0.2 (1.7)	−0.9 (1.4)	−0.7 (2.0)	−1.3, −0.1	**0.036**	0.33

Participant Training

PLOS ONE

RESEARCH ARTICLE

Accurate pain reporting training diminishes the placebo response: Results from a randomised, double-blind, crossover trial

Roi Treister[1,2,3]*, Oluwadolapo D. Lawal[3], Jonathan D. Shecter[3], Nevil Khurana[3], John Bothmer[4], Mark Field[4], Steven E. Harte[5], Grant H. Kruger[5,6], Nathaniel P. Katz[3,7]

Training using calibrated noxious stimuli reduces placebo responses in PDN patients in a crossover RCT of pregabalin:

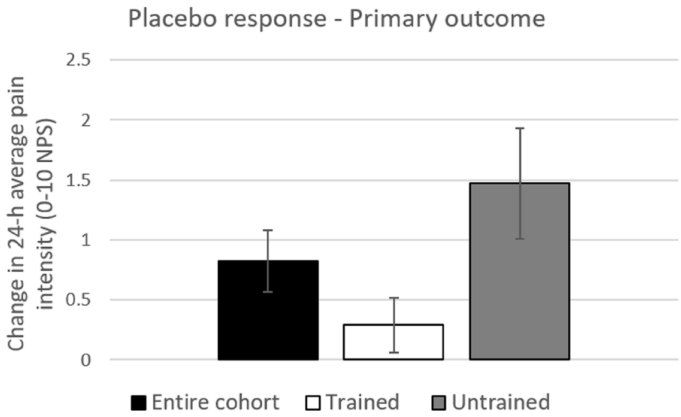


Fig 4. The placebo response in the entire cohort, trained and untrained subjects—Primary outcome measure. Change in placebo was calculated as difference between pain scores in the placebo arm (pre-minus post treatment). Black bars represent changes in pain in the entire cohort. White and Black bars represent changes in pain in the trained (n = 28) and untrained (n = 23) sub-cohorts, respectively. * = P<0.05; Error bars are Standard Error of the Mean (SEM).

PAIN

Pain intensity rating training: results from an exploratory study of the ACTTION PROTECCT system

Shannon M. Smith[a,*], Dagmar Amtmann[b], Robert L. Askew[c], Jennifer S. Gewandter[a], Matthew Hunsinger[d], Mark P. Jensen[b], Michael P. McDermott[e,f], Kushang V. Patel[g], Mark Williams[a], Elizabeth D. Bacci[h], Laurie B. Burke[i,j], Christine T. Chambers[k,l,m], Stephen A. Cooper[n], Penney Cowan[o], Paul Desjardins[p], Mila Etropolski[q], John T. Farrar[r,s,t], Ian Gilron[u,v], I-zu Huang[w], Mitchell Katz[x], Robert D. Kerns[y,z,aa,bb], Ernest A. Kopecky[cc], Bob A. Rappaport[dd], Malca Resnick[ee], Vibeke Strand[ff], Geertrui F. Vanhove[w], Christin Veasley[gg], Mark Versavel[hh], Ajay D. Wasan[ii,jj], Dennis C. Turk[g], Robert H. Dworkin[a,f,kk,ll]

Among participants with chronic pain, training in accurate rating (e.g., instruction about anchors, pain intensity, pain duration, etc. with practice rating least, worst, and average daily pain) reduced rating errors:

	All		Group T+		Group T		Group C	
	Number of ratings	%	Number of ratings	%	Number of ratings	%	Number of ratings	%
Total number of ratings collected	4364		1537		1319		1508	
Least ≤ Average ≤ Worst (correct order)	4198	96%	1523	99%	1272	96%	1403	93%

Other Outcomes: Neuropathic Pain Screening Tools

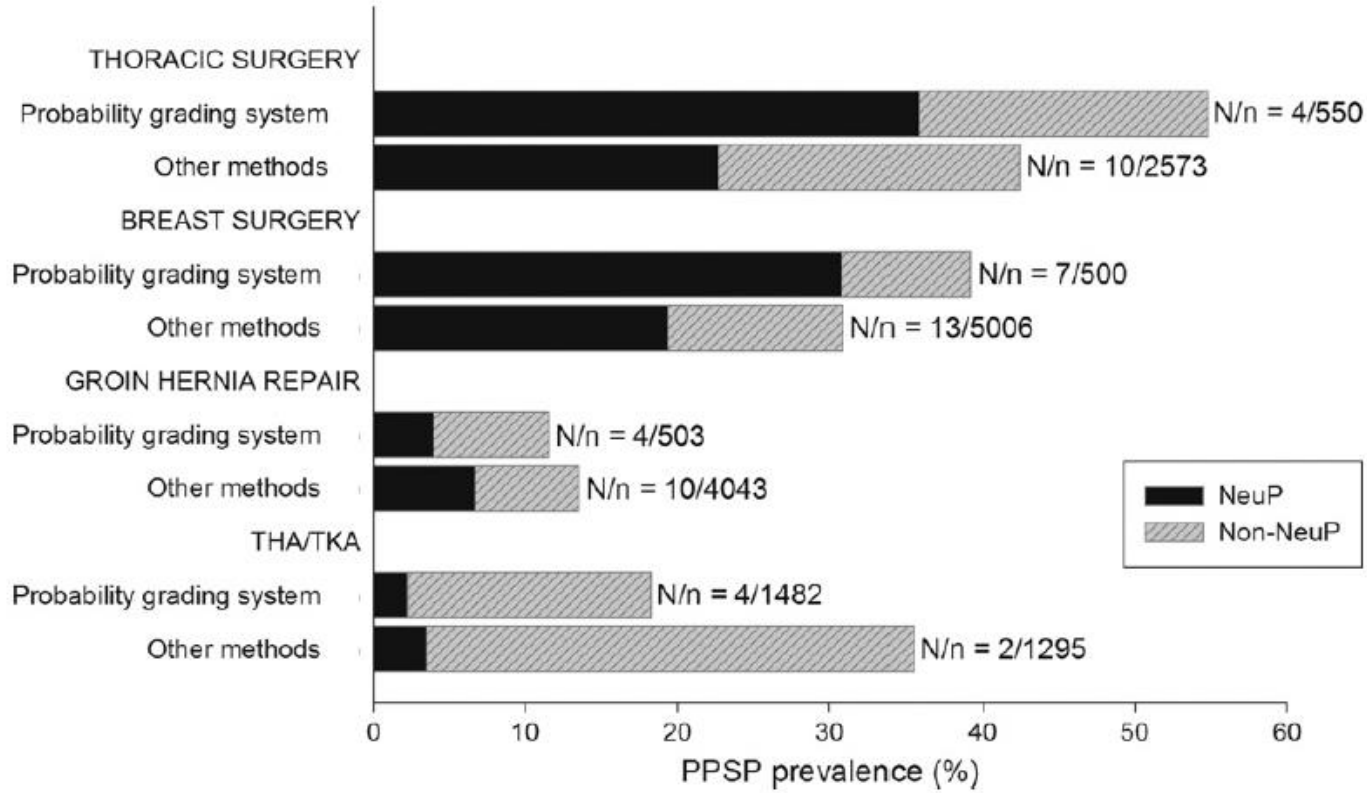


Fig. 3. Neuropathic PPSP prevalence. Comparison of absolute NeuP vs non-NeuP prevalence assessed by NeuP probability grading system and by other methods. The number of studies/patients based on which the mean prevalence was calculated are provided on the right side of each bar. PPSP, persistent postsurgical pain; NeuP, neuropathic pain; THA, total hip arthroplasty; TKA, total knee arthroplasty.

Emotional Function

Hospital Anxiety and Depression Scale: Brief, face valid, minimally confounded by physical symptoms, very well-validated, well-normed, established cutoffs, provides scores for anxiety and depression.

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY

PUBLISHED BY ELSEVIER
The Journal of Pain, Vol 17, No 9 (September), Suppl. 2, 2016: pp T21-T49
Available online at www.jpain.org and www.sciencedirect.com

Assessment of Psychosocial and Functional Impact of Chronic Pain

Dennis C. Turk,* Roger B. Fillingim,† Richard Ohrbach,‡ and Kushang V. Patel*

Chart 1 – Hospital Anxiety and Depression Scale

This questionnaire will help your physician to know how you are feeling. Read every sentence. Place an "X" on the answer that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important.

A 1) I feel tense or wound up:
- 3 ( ) Most of the time
- 2 ( ) A lot of the time
- 1 ( ) From time to time
- 0 ( ) Not at all

D 2) I still enjoy the things I used to enjoy
- 0 ( ) Definitely as much
- 1 ( ) Not quite so much
- 2 ( ) Only a little
- 3 ( ) Hardly at all

A 3) I get a sort of frightened feeling as if something awful is about to happen
- 3 ( ) Very definitely and quite badly
- 2 ( ) Yes, but not too badly
- 1 ( ) A little, but it doesn't worry me
- 0 ( ) Not at all

D 4) I can laugh and see the funny side of things
- 0 ( ) As much as I always could
- 1 ( ) Not quite as much now
- 2 ( ) Definitely not so much now
- 3 ( ) Not at all

A 5) Worrying thought goes through my mind
- 3 ( ) A great deal of the time
- 2 ( ) A lot of the time
- 1 ( ) From time to time but not too often
- 0 ( ) Only occasionally

D 6) I feel cheerful
- 3 ( ) Not at all
- 2 ( ) Not often
- 1 ( ) Sometimes
- 0 ( ) Most of the time

A 7) I can seat at ease and feel relaxed
- 0 ( ) Definitely
- 1 ( ) Usually
- 2 ( ) Not often
- 3 ( ) Not at all

D 8) I feel as I am slowed down
- 3 ( ) Nearly all the time
- 2 ( ) Very often
- 1 ( ) Sometimes
- 0 ( ) Not at all

A 9) I get a sort of frightened feeling like butterflies in the stomach
- 0 ( ) Not at all
- 1 ( ) Occasionally
- 2 ( ) Quite often
- 3 ( ) Very often

D 10) I have lost interest in my appearance
- 3 ( ) Definitely
- 2 ( ) I don't take so much care as I should
- 1 ( ) I may not take quite as much care
- 0 ( ) I take just as much care as ever

A 11) I feel restless, as if I had to be on the move
- 3 ( ) Very much indeed
- 2 ( ) Quite a lot
- 1 ( ) Not very much
- 0 ( ) Not at all

D 12) I look forward with enjoyment to things
- 0 ( ) As much as I ever did
- 1 ( ) Rather less than I used to
- 2 ( ) Definitely less than I used to
- 3 ( ) Hardly at all

A 13) I get sudden feeling of panic
- 3 ( ) Very often indeed
- 2 ( ) Quite often
- 1 ( ) Not very often
- 0 ( ) Not at all

D 14) I can enjoy a good TV or radio program or book
- 0 ( ) Often
- 1 ( ) Sometimes
- 2 ( ) Not often
- 3 ( ) Very seldom

“Adverse Events”

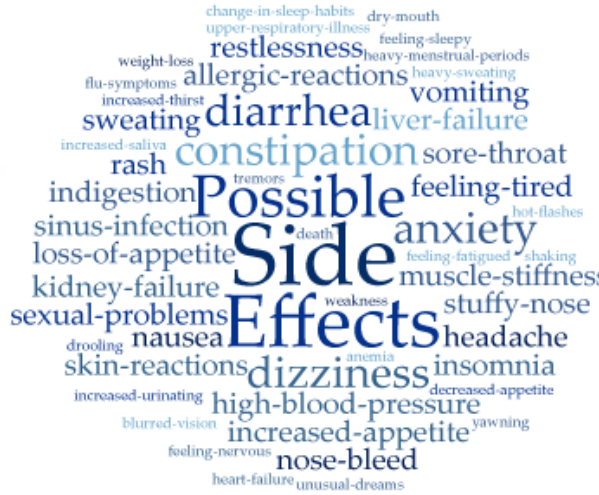


Table 1
Recommended core outcome measures for clinical trials of chronic pain treatment efficacy and effectiveness

Symptoms and adverse events
Passive capture of spontaneously reported adverse events and symptoms and use of open-ended prompts

Within the context of pharmacologic investigations, adverse events have been defined as “any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment” (International Conference on Harmonization, 1995b).

IMMPACT recommends that, at a minimum, passive capture of spontaneously reported events and the use of open-ended prompts should be used in chronic pain clinical trials to assess adverse events. In describing the results of clinical trials, the incidence of individual adverse events and serious adverse events should be reported for each treatment group . . .

Active capture using structured interviews or questionnaires to assess specific symptoms and adverse events that are relevant to the disorder or treatment being studied will often be more sensitive and more informative than passive capture or general inquiries (e.g. Anderson and Testa, 1994; Edwards et al., 1999). Depending on the objectives of a chronic pain clinical trial, active capture of selected symptoms and adverse events can be conducted at periodic intervals throughout the trial, including baseline and the conclusion of the trial, ideally by the same investigator. **It is important to recognize that the frequency, duration, intensity, distress, importance to the patient, impact on daily function, and investigator and patient causal attributions can be assessed for symptoms and adverse events.**

Physical Function: *Recent Recommendations*

Comprehensive Review
PAIN

Assessment of physical function and participation in chronic pain clinical trials: IMMPACT/ OMERACT recommendations

Ann M. Taylor[a], Kristine Phillips[b], Kushang V. Patel[c], Dennis C. Turk[c], Robert H. Dworkin[d], Dorcas Beaton[e,f], Daniel J. Clauw[g], Monique A.M. Gignac[h], John D. Markman[i], David A. Williams[g], Shay Bujanover[j], Laurie B. Burke[k,l], Daniel B. Carr[m], Ernest H. Choy[n], Philip G. Conaghan[o,p], Penney Cowan[q], John T. Farrar[r], Roy Freeman[s], Jennifer Gewandter[d], Ian Gilron[t], Veeraindar Goli[u,v], Tony D. Gover[w], J. David Haddox[x], Robert D. Kerns[y,z], Ernest A. Kopecky[aa], David A. Lee[bb], Richard Malamut[cc], Philip Mease[dd,ee,ff], Bob A. Rappaport[gg], Lee S. Simon[hh], Jasvinder A. Singh[ii,jj], Shannon M. Smith[d], Vibeke Strand[kk], Peter Tugwell[ll], Gertrude F. Vanhove[mm], Christin Veasley[nn], Gary A. Walco[c], Ajay D. Wasan[oo], James Witter[pp]

"Generic" and disease-specific measures:

Table 6

Summary of recommendations.

Physical functioning assessments should be developed within a conceptual model
Patient input should be included in the earliest stages of the development process for any outcome measure
Investigators should assess the appropriateness of any measure of physical functioning that they are considering for the specific population they are studying
Investigators should assess the appropriateness of a given measure for the specific research objectives of the research
Investigators should give consideration to use of disease-specific measures combined with generic measures of physical functioning when designing a chronic pain clinical trial
Consideration should be given to use of a combination of both types of physical functioning outcomes, that is, patient-reported measures and more objective assessments of activity or performance
Investigators should consider actigraphy as an objective measure of physical activity if they can demonstrate that the measure captures the physical activity of interest

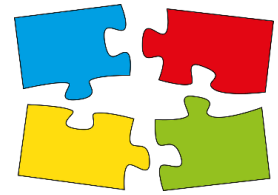
WOMAC

What degree of difficulty do you have due to pain, discomfort or arthritis…".
Using a five-point scale with the choices of none, mild, moderate, severe, or extreme.

Physical Function	1. Descending stairs	0	1	2	3	4
	2. Ascending stairs	0	1	2	3	4
	3. Rising from sitting	0	1	2	3	4
	4. Standing	0	1	2	3	4
	5. Bending to floor	0	1	2	3	4
	6. Walking on flat surface	0	1	2	3	4
	7. Getting in / out of car	0	1	2	3	4
	8. Going shopping	0	1	2	3	4
	9. Putting on socks	0	1	2	3	4
	10. Lying in bed	0	1	2	3	4
	11. Taking off socks	0	1	2	3	4
	12. Rising from bed	0	1	2	3	4
	13. Getting in/out of bath	0	1	2	3	4
	14. Sitting	0	1	2	3	4
	15. Getting on/off toilet	0	1	2	3	4
	16. Heavy domestic duties	0	1	2	3	4
	17. Light domestic duties	0	1	2	3	4

Evaluating "Objective" Physical Function Measures?

- Patient-reported outcome (PRO) measures are "subjective" and may under- or over-estimate actual activity or function
- In performance-based tests, patients are asked to do activities that are evaluated in a standardized manner
  - ✓ for example, time to complete the activity or an observer evaluation of adequacy of performance
- When associations between these two different types of measures are examined, there are only modest correlations
- Do subjective and objective measures therefore assess different aspects of physical activity and function?



Application in a Trial

ORIGINAL ARTICLE

Assessment of Pain and Activity Using an Electronic Pain Diary and Actigraphy Device in a Randomized, Placebo-Controlled Crossover Trial of Celecoxib in Osteoarthritis of the Knee

Jeremiah Trudeau, PhD*,†; Richard Van Inwegen, PhD*; Thomas Eaton, PhD‡; Gajanan Bhat, PhD*,§; Florence Paillard, PhD¶; Dik Ng, PhD**; Keith Tan, PhD**; Nathaniel P. Katz, MD, MS*,††

Results: Sixty-three patients were randomized and 47 completed the study. The WOMAC pain subscale was the most responsive of all five pain measures. Pain–activity composites resulted in a statistically significant difference between celecoxib and placebo but were not more responsive than pain measures alone. However, a composite responder defined as having 20% improvement in pain or 10% improvement in activity yielded much larger differences between celecoxib and placebo than with pain scores alone. Actigraphy was more responsive than the WOMAC function scale, possibly due to lower placebo responsiveness.

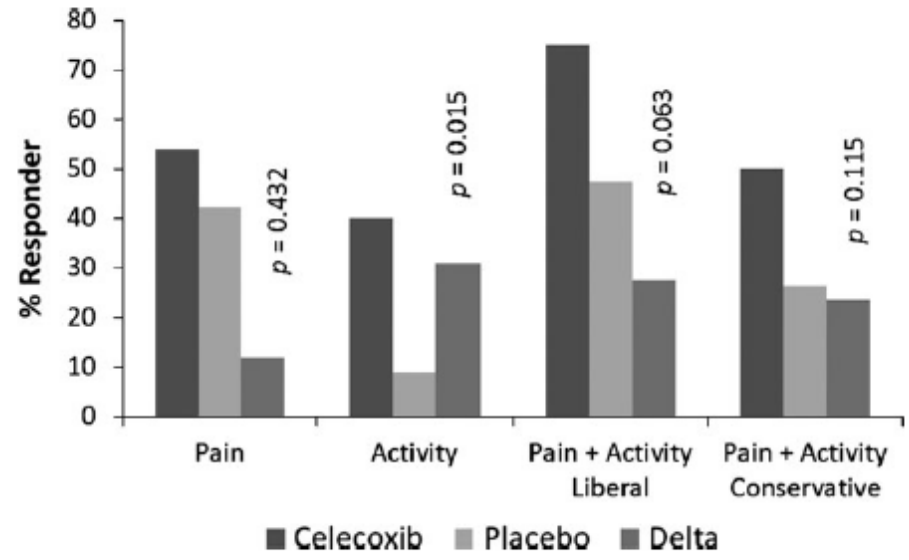


Figure 4. Period 1 responder rates as determined by the electronic pain diary/actigraphy device (e-PDAD). Pain = % of patients with a 20% improvement in pain regardless of change in activity. Activity = % of patients with 10% improvement of activity regardless of change in pain scores. Pain + Activity Liberal = % of subjects with a 20% improvement in pain or a 10% reduction in activity. Pain + Activity Conservative = % of subjects with a 20% improvement in pain and a 10% reduction in activity.

Composite Outcomes

Minimal association between pain and function in neuropathic pain

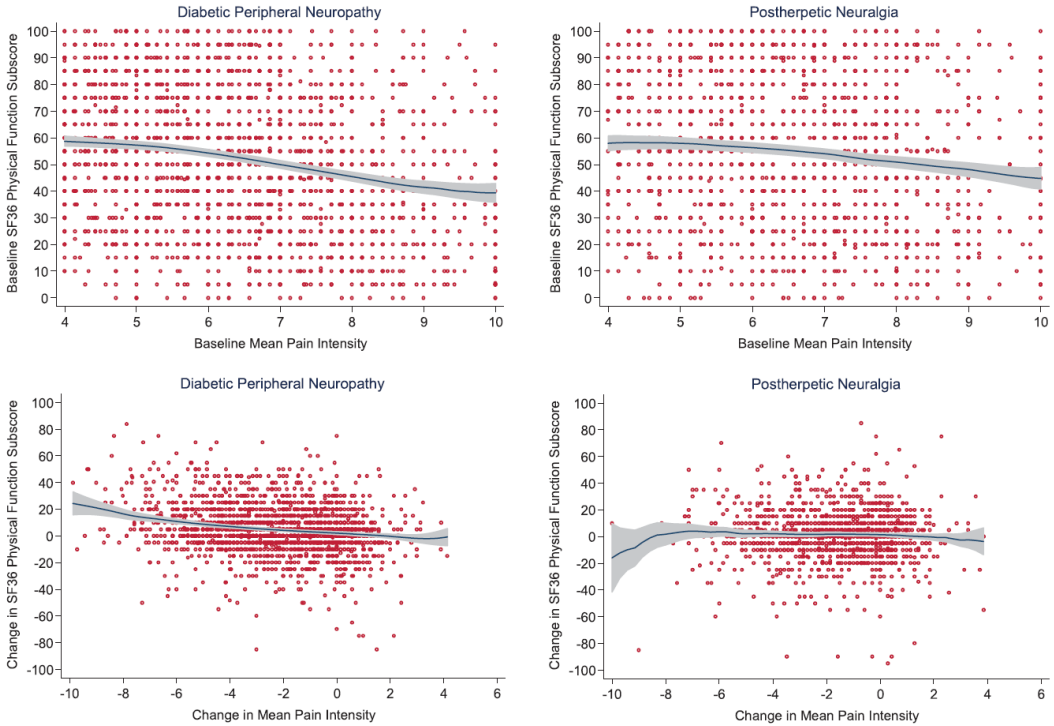


Figure 1. Baseline and longitudinal (pre-to-post treatment) relationships between pain intensity and physical function in randomized clinical trials of gabapentin, pregabalin, and duloxetine for diabetic peripheral neuropathy and postherpetic neuralgia. Red circles represent observations of individual study participants; the locally weighted regression line is shown in navy blue; and the 95% confidence interval band is shown in shaded gray.

PAIN

Evaluation of composite responder outcomes of pain intensity and physical function in neuropathic pain clinical trials: an ACTTION individual patient data analysis

Kushang V. Patel[a,*], Robert Allen[b], Laurie Burke[c], John T. Farrar[d], Jennifer S. Gewandter[e], Ian Gilron[f], Nathaniel P. Katz[g], John D. Markman[e], Scott F. Marshall[h], Malca Resnick[i], Andrew S.C. Rice[j], Michael C. Rowbotham[k], Shannon M. Smith[e], Geertrui F. Vanhove[l], Ajay D. Wasan[m], Shuyu Zhang[n], Robert H. Dworkin[e], Dennis C. Turk[a]

≥50% improvement in pain intensity, or
≥20% improvement in pain intensity **and**
≥30% improvement in physical function

NNTs 4.2 – 4.8

	≥50% reduction in pain intensity, no. (%)	Risk ratio (95% CI)	Number needed to treat* (95% CI)
Gabapentin			
2 DPN trials (N = 408)			
Placebo (n = 158)	36 (22.8)	1.0	
Gabapentin (n = 250)	101 (40.4)	1.8 (1.1-2.8)	5.7 (3.8-12.0)
2 PHN trials (N = 563)			
Placebo (n = 227)	30 (13.2)	1.0	
Gabapentin (n = 336)	106 (31.6)	2.4 (1.6-3.6)	5.5 (4.0-8.8)
Pregabalin			
5 DPN trials (N = 1203)			
Placebo (n = 426)	91 (21.4)	1.0	
Pregabalin (n = 777)	297 (38.2)	1.8 (1.3-2.5)	5.9 (4.6-8.7)
4 PHN trials (N = 950)			
Placebo (n = 346)	47 (13.6)	1.0	
Pregabalin (n = 604)	186 (30.8)	2.4 (1.6-3.5)	5.8 (4.5-8.4)

Timing of Outcomes Assessment

Table 1

Recommendations.

Models	Treatment timing	Outcome measures	Assessment timing
CPSP	Preoperative Perioperative Duration of acute pain recovery (based on natural history of recovery for each surgical model)	Presence vs absence of pain Presence vs absence of "clinically meaningful" pain Pain intensity at rest Pain intensity upon movement and specific activities (well defined) Pain qualities Secondary end points: physical and emotional functioning	24-48 h after surgery 3, 6, and 12 mo Surgery-specific times based on natural history c acute to chronic pain transition
PHN	As soon as possible after rash onset (but ≤ 7 d) Duration of acute HZ pain (≤ 30 d from rash onset)	Presence vs absence of pain in the area of the rash Presence vs absence of "clinically meaningful" pain in the area of the rash Pain intensity at HZ rash location Pain qualities at HZ rash location Secondary end points: physical and emotional functioning	3-4 mo after rash onset
CLBP	As soon as possible after an acute back pain episode (within 3 wk) Duration of acute pain (~ 3 mo)	Presence vs absence of chronic pain as defined by the NIH Task Force[37] Pain intensity AUC of pain assessments between 3 mo and final time point Secondary end points: physical and emotional functioning	3, 6, and 12 mo
Painful CIPN	Prechemotherapy Duration of chemotherapy (either daily or only proximal to chemotherapy infusions)	Presence vs absence of pain Presence vs absence of "clinically meaningful" pain Secondary end points: physical and emotional functioning	3 and 6 mo

AUC, area under the curve; CIPN, chemotherapy-induced peripheral neuropathy; CLBP, chronic low back pain; CPSP, Chronic postsurgical pain; HZ, herpes zoster; PHN, postherpetic neuralgia.

"It may be difficult to identify clinically meaningful levels of pain for the different chronic pain conditions given that there has been little systematic examination of patient-reported assessments of the long-term impact of different levels of pain. Future studies should investigate patient opinions regarding the minimal pain intensity and duration that would be considered to be clinically meaningful in relation to the probability of developing such chronic pain as well as risks and costs of the potential preventive treatment (e.g., what level and nature of side effects would the patient be willing to tolerate for an intervention that reduced the probability of a certain intensity of pain in the future by a specified amount or period). Better understanding of how to define the minimal threshold of chronic pain that would be considered clinically meaningful will allow researchers to more accurately determine the necessary sample sizes for RCTs of preventive analgesic treatments."

Importance of Intervention Duration/Timing When Assessing Outcomes

(Treatments have different time courses:)

Arthritis Care & Research
Vol. 72, No. 5, May 2020, pp 641–651
DOI 10.1002/acr.23884

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

Duration of Symptom Relief and Early Trajectory of Adverse Events for Oral Nonsteroidal Antiinflammatory Drugs in Knee Osteoarthritis: A Systematic Review and Meta-Analysis

Mikala C. Osani, Elizaveta E. Vaysbrot, Mengyu Zhou, Timothy E. McAlindon, and Raveendhara R. Bannuru

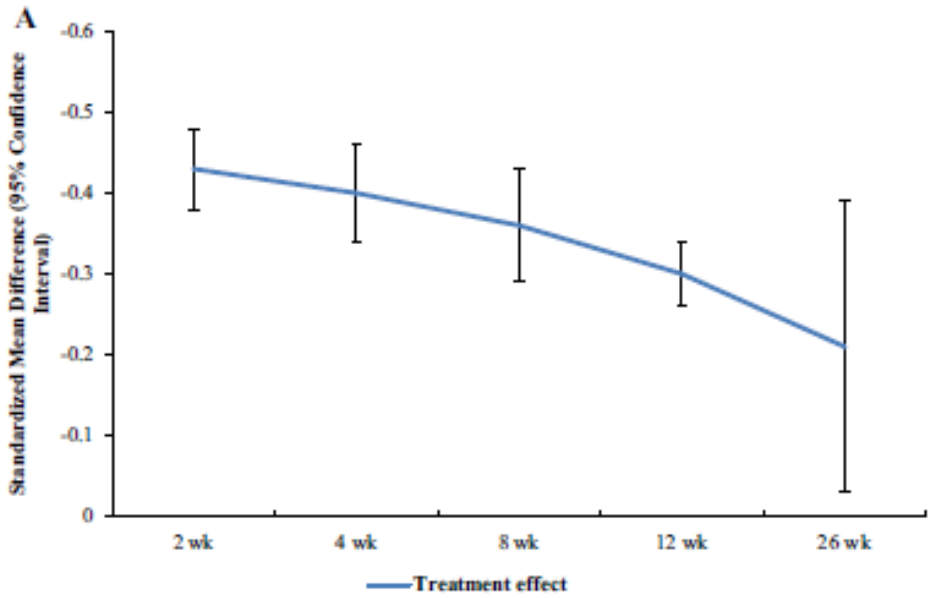


Figure 1. Trajectory of overall effects of NSAIDs on pain (A)

Journal of Pain Research

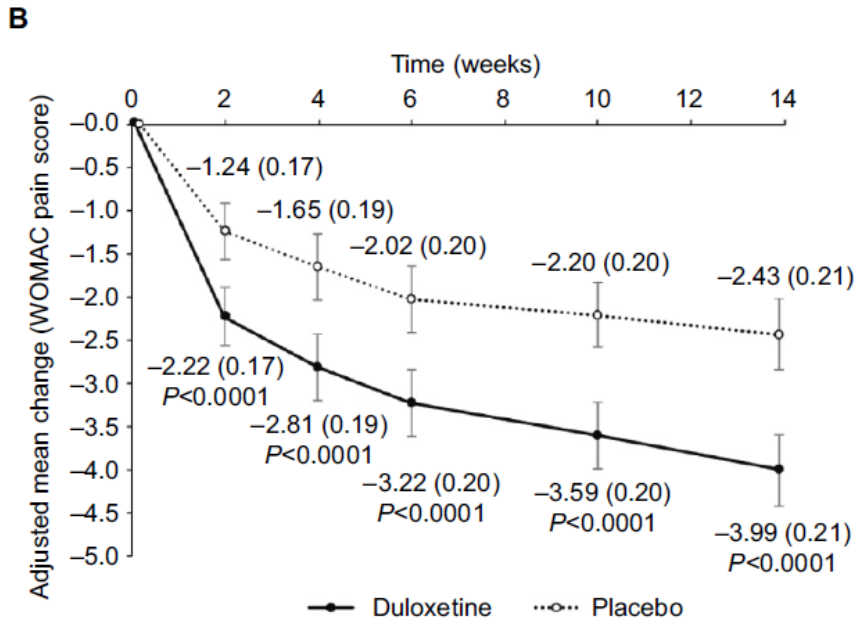
Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

A randomized, double-blind, placebo-controlled Phase III trial of duloxetine in Japanese patients with knee pain due to osteoarthritis

Yuji Uchio[1]
Hiroyuki Enomoto[2]
Levent Alev[2]
Yuki Kato[3]
Hiroyuki Ishihara[3]
Toshinaga Tsuji[4]
Toshimitsu Ochiai[5]
Shinichi Konno[6]



Outcomes for Chronic Pain Prevention Studies

Postsurgical follow-up screening for CPSP occurred at 1-12 months after breast tumor resection. The criteria used in CPSP screening differed; 3 trials relied on verbal report of absence/presence of pain symptoms only; 2 used a predefined threshold of pain severity score; 2 studies differentiated between neuropathic and non-neuropathic pain.

Table 2

Adherence to IMMPACT recommendations.

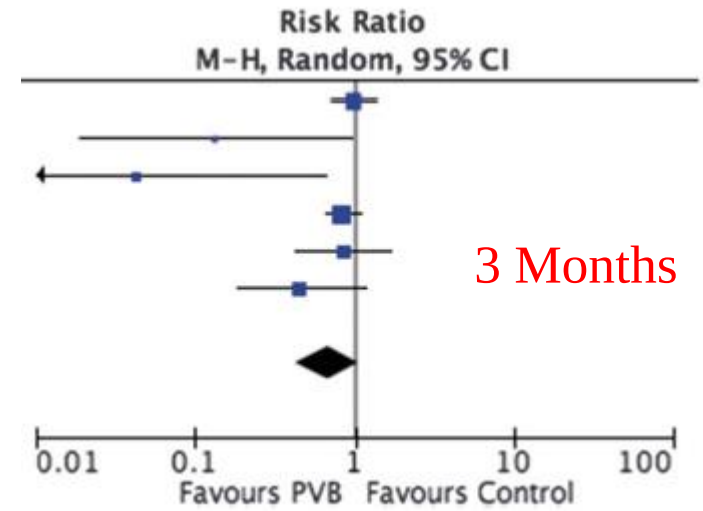
IMMPACT recommendation	Kairaluoma (2006)	Iohom (2006)	Ibarra (2011)	Elkaradawy (2012)	Lee (2013)	Karmakar (2014)	Abdallah (2015)	Gracio (2016)	Xu (2016)
Outcome selection									
Assessment of genetic factors					X				
Measuring the cost of the preventive treatment (side effects)		X	X		X	X	X	X	
Reporting rescue pain medications during the follow-up period	X	X				X	X	X	X
Chronic pain (>3 months) intensity Reported as NRS score	X						X		
Reporting dynamic component of CPSP	X					X			
Reporting chronic pain qualities (characterization) and pain affect	X	X		X			X		
Measurement of temporal aspect of pain	X			X	X	X	X		
Inclusion of 3-, 6-, and 12-month assessments for CPSP									
Inclusion of neuropathic pain measures				X			X	X	
Measurement of disease-specific functional outcomes (eg, shoulder function)						X		X	
Reporting patient satisfaction with treatment and rating global improvement						X			
Results interpretation									
Examining the impact of chronic pain on physical and emotional functioning, quality of life, as well as sleep						X	X	X	
Identifying clinically important differences in CPSP and other outcomes							X		

CPSP, chronic postsurgical pain; NRS, numeric rating scale.

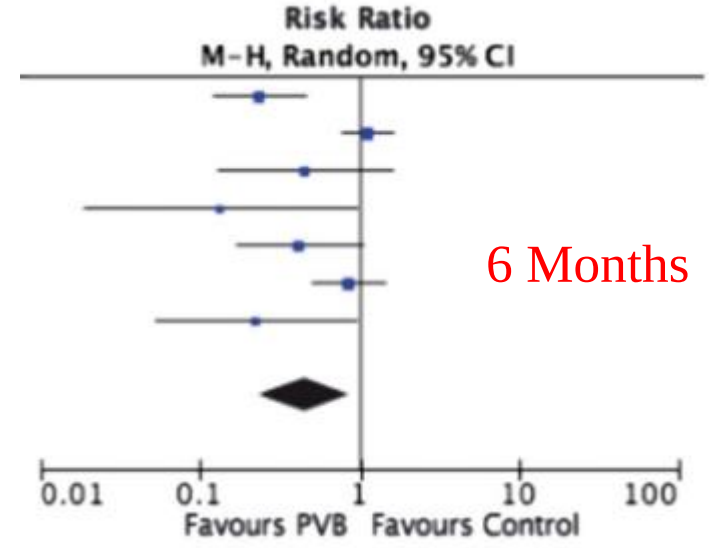
Systematic Reviews and Meta-Analyses
PAIN

Should thoracic paravertebral blocks be used to prevent chronic postsurgical pain after breast cancer surgery? A systematic analysis of evidence in light of IMMPACT recommendations

Nasir Hussain[a], Uma Shastri[b], Colin J.L. McCartney[c,d], Ian Gilron[e], Roger B. Fillingim[f], Hance Clarke[g,h], Joel Katz[g,h,i], Peter Juni[j,k], Andreas Laupacis[l,m,n], Duminda Wijeysundera[g,h,l,n], Faraj W. Abdallah[c,d,g,n,*]



3 Months



6 Months

Current Example:

"The goal of the Acute to Chronic Pain Signatures (A2CPS) program is to develop a set of objective biomarkers that provide "signatures" to predict if chronic pain is likely to develop after acute pain. Such signatures are greatly needed as prevention of chronic pain after an acute pain event is a major challenge in pain management. For most people, acute pain resolves as the injury that caused it heals. Yet in many other people, acute pain from an injury, surgery, or disease persists beyond the initial insult, and lasts for years or throughout life. The number of people who transition from acute to chronic pain after an acute pain event is high, and this high prevalence of chronic pain in the US has in part contributed to the current opioid epidemic . . ."

Primary Chronic Pain Outcome: Categorical measurement, at 6 months after surgery, of worst pain greater than 3/10 over the past 24 hours

Clinician Preferences for Outcome Reporting

CMAJ RESEARCH

Do clinicians understand the size of treatment effects? A randomized survey across 8 countries

Bradley C. Johnston PhD, Pablo Alonso-Coello MD PhD, Jan O. Friedrich MD, Reem A. Mustafa MD PhD, Kari A.O. Tikkinen MD PhD, Ignacio Neumann MD, Per O. Vandvik MD PhD, Elie A. Akl MD PhD, Bruno R. da Costa PhD, Neill K. Adhikari MD, Gemma Mas Dalmau MD, Elise Kosunen MD PhD, Jukka Mustonen MD PhD, Mark W. Crawford MD, Lehana Thabane PhD, Gordon H. Guyatt MD

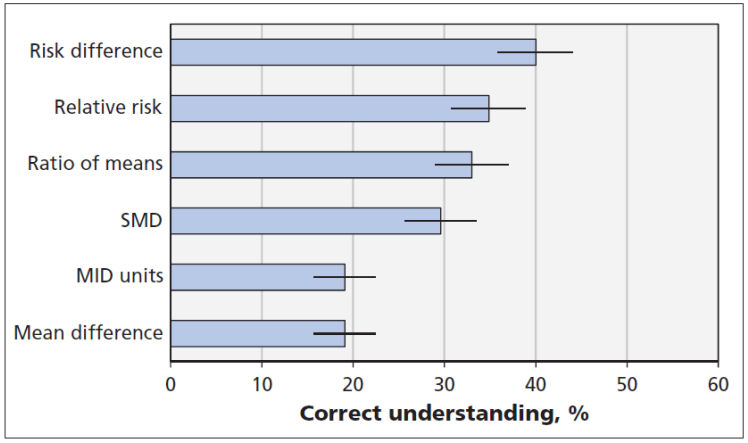


Figure 1: Respondents' understanding of the magnitude of the treatment effect for each of 6 statistical formats used to present continuous outcomes from meta-analyses. Higher percentages represent greater understanding;

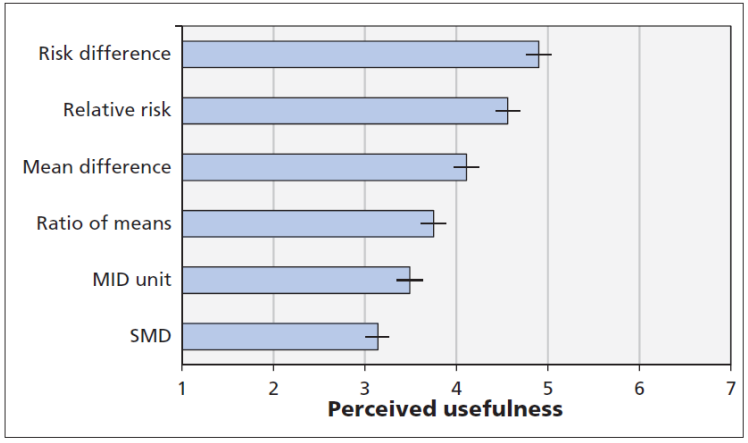
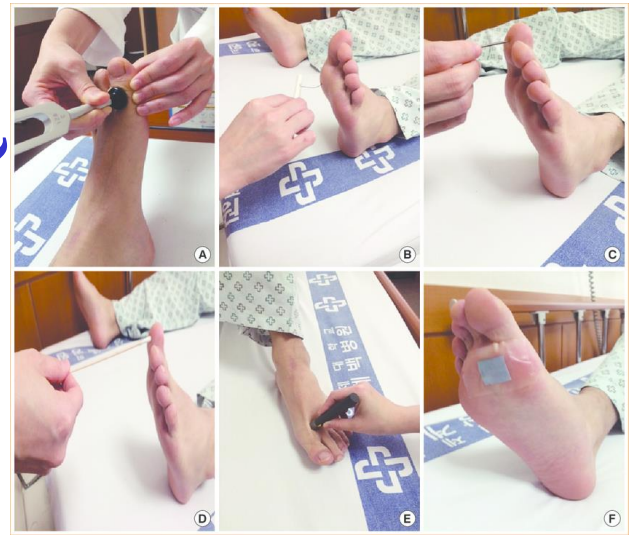


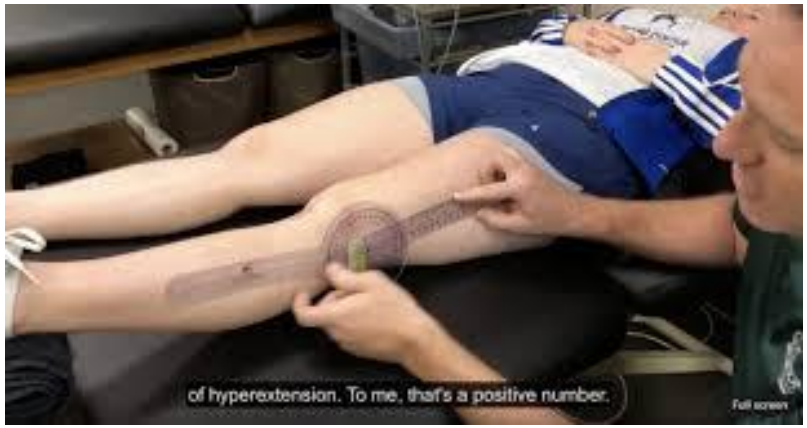
Figure 2: Perceived usefulness of each statistical format for clinical decision-making. Higher scores represent higher perceived usefulness; error bars = 95% confidence intervals. Mean difference = mean difference in natural units, MID = minimal important difference, SMD = standardized mean difference.

Approach	Description
SMD (standardized mean difference)	When results of trials are reported using different units (e.g. different instruments to measure the same construct), authors typically report differences between intervention and control groups in standard deviation units, an approach known as the SMD approach. This involves dividing the mean difference in each trial by the pooled standard deviation for that trial's outcome.
MID (minimal important difference units)	The pooled mean difference is presented in MID units. This involves dividing the mean difference by the minimal important difference specific to the continuous measure used for each trial (MIDs can be imputed for instruments without an established MID to obtain an estimate in MID rather than SD units which may be more intuitive to clinicians.
MD (mean difference in natural units)	When results of trials are reported using identical units (e.g. all trials used the same instrument to measure physical function or pain), the most straightforward method pools the reported data directly using the MD approach. This method involves calculating and pooling the absolute difference between the mean values in intervention and control groups (i.e. the mean difference in natural units) for each trial. If different instruments are used, a linear transformation of trial data to most familiar instrument can also be used.
RoM (ratio of means)	The ratio between the mean responses in the intervention and control group. Involves dividing the mean value in the intervention group by the mean value in the control group for each trial to present result as percentage changes.
RR (relative risk)	Obtain proportion above threshold in both groups and calculate relative binary treatment effect estimate. Involves converting the continuous outcomes to binary outcomes for each study and then pooling these binary outcomes using standard relative risk or risk difference approaches. Requires deciding on a threshold value. If MID estimate is available, this should be considered the threshold of interest. If no MID is available, the chosen threshold may be somewhat arbitrary. For example, using a visual analogue 10-point scale to measure pain, one might choose a score of 7 or higher to classify the patient as having "severe pain." Converting a continuous measure to a binary measure discards information (i.e. both a patient with a pain score of 10 and a patient with a pain score of 7 will be classified as having "severe pain").
RD (risk difference)	Obtain proportion above threshold in both groups and calculate the absolute binary treatment effect estimate. Otherwise, see description for RR above.

Inclusion of Novel Outcome Measures ?

Bedside QST





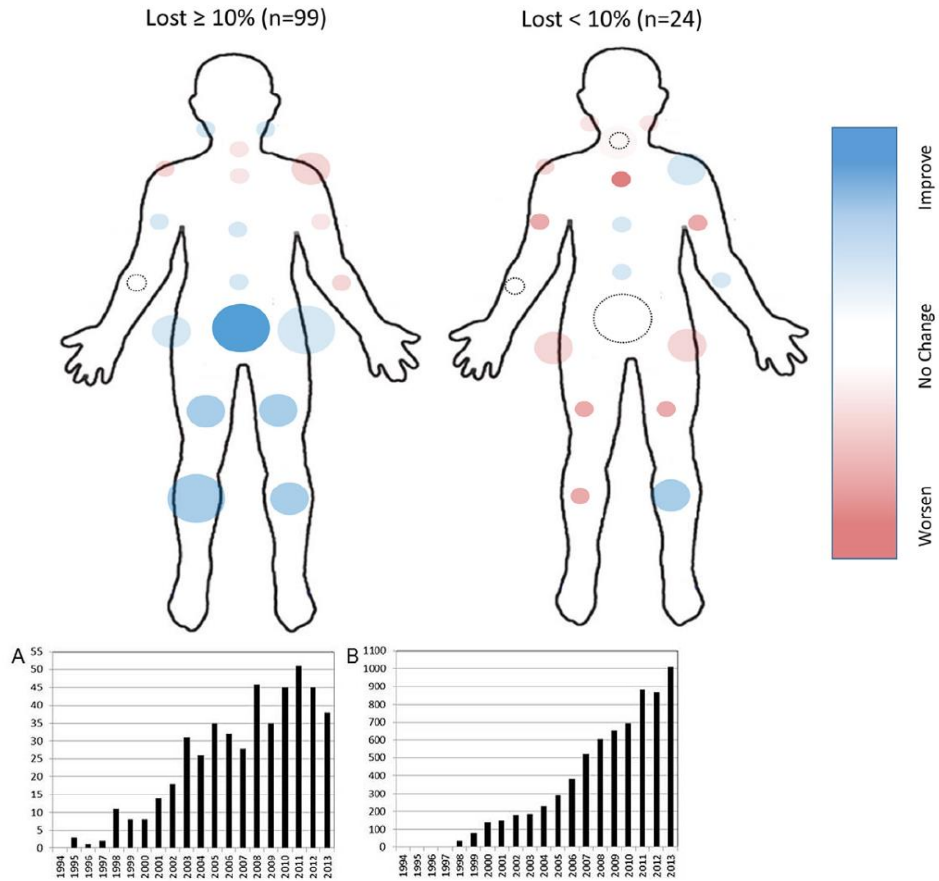


Figure 1 (A) Annual indexed publications following a search of "pain" and "spirituality" from 1994 to 2013. (B) Annual indexed citations following a search of "pain" and "spirituality" from 1994 to 2013.

(182) What do Patients with Acute and Chronic Pain Think about Rating the Intensity of their Pain? Insights from ACTTION's QUALITE-Pain Concept Elicitation Interviews

S. Smith et al. Journal of Pain, 2019-04-01, Volume 20, Issue 4, Pages S21-S21