From mechanisms to medicines: what ACTTION can be taken to accelerate analgesic drug development?

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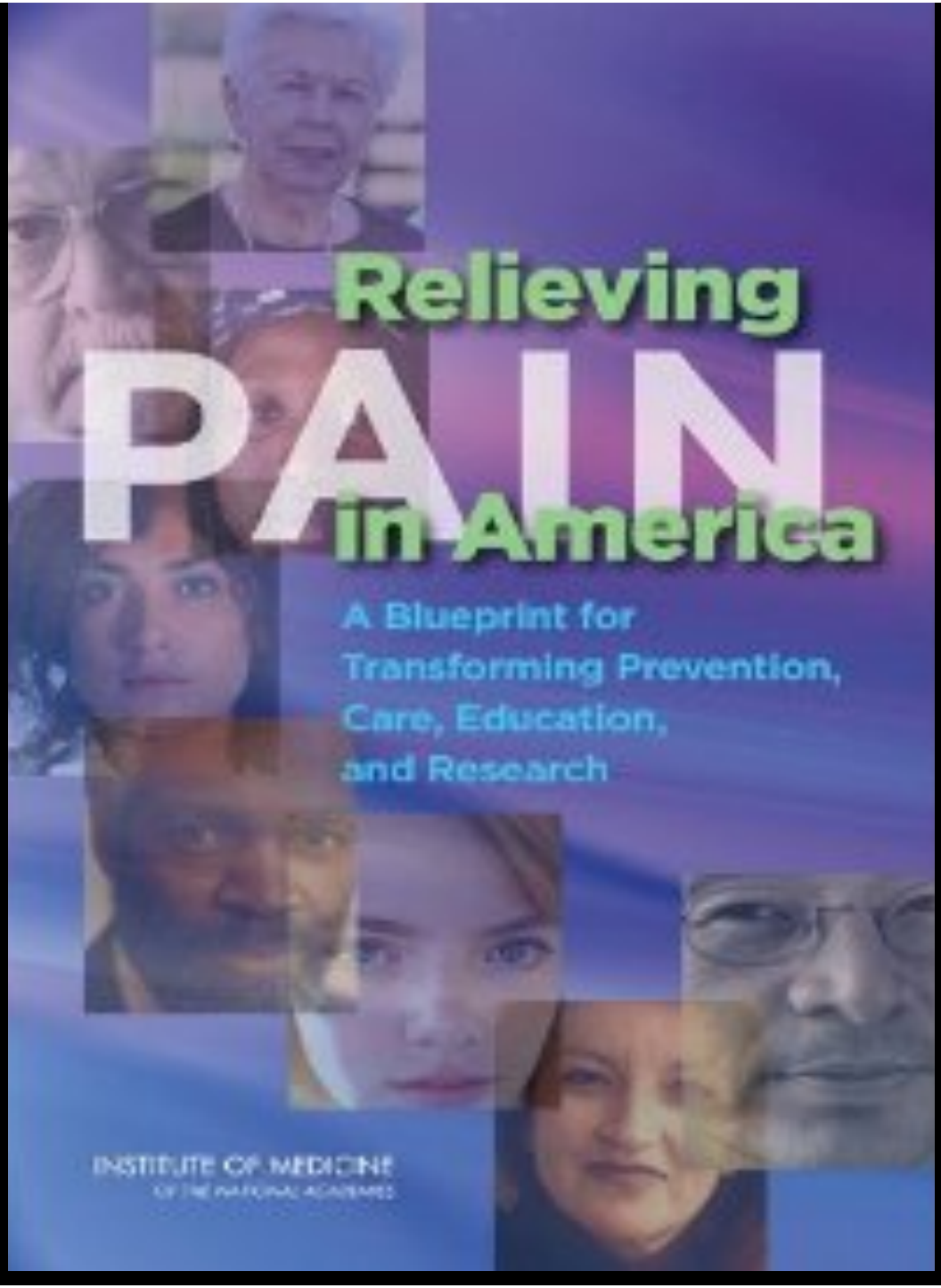
Relieving
PAIN
in America
A Blueprint for
Transforming Prevention,
Care, Education,
and Research
INSTITUTE OF MEDICINE

- **More than 100 million Americans have pain that persists for weeks to years.**
- **The total financial costs of this epidemic are $560 billion to $635 billion per year, not including pain in children, in long-term facilities, the military, or prison.**
- **Annual U.S. expenditures related to pain (including direct medical costs and lost wages) are higher than those for cancer, heart disease, and diabetes *combined*.**
- **In a survey of 117 medical schools, some reported including only a few sessions on pain in their curricula.**

Unmet needs: objectives and opportunities for improved analgesic treatments

1. Pain relief in a higher percentage of patients
2. Greater magnitude of pain relief in patients who do respond (e.g., percentage ≤ mild pain)
3. Greater benefits on health-related quality of life
4. Better safety and tolerability
5. Few or no drug interactions
6. Greater convenience and compliance
7. Mechanism-based treatment approaches
8. Prevention of chronic pain

Mechanism	Symptom	Target	Drug
Peripheral sensitization (Increased transduction sensitivity, increased terminal excitability)	Pressure (static) hyperalgesia Thermal hyperalgesia Spontaneous pain	VR-1	Capsaicin (VR-1 desensitization) *VR-1 antagonists*
		TTXr-VGSC	*TTXr-VGSC blockers*
		NGF/TrkA	*NGF-antagonists*
		Bradykinin	*Bradykinin antagonists*
Ectopic discharge	**Spontaneous pain (e.g., burning)**	**VGSC**	**Na+ channel blockers - carbamazepine, lamotrigine**
		K^+ channels	*K^+ channel activators*
Sympathetically maintained pain (α–receptor expression, sympathetic sprouting)	Spontaneous pain	α1-receptor	Phentolamine Guanethidine block
Central sensitization	**Tactile (dynamic) hyperalgesia**	**NMDA-R**	**NMDA antagonists - ketamine, amantadine, dextromethorphan**
		nNOS	*nNOS inhibitors*
		PKCγ	*PKCγ inhibitors*
		MAPK/ERK	*MEK inhibitors*
Reduced inhibition **Increased transmission**	Spontaneous pain Hyperalgesia	Receptors MOR, α2, GABA, adenosine, P2X3, *kainate, mGluR, CCK, nAChR, CB2* N-type Ca^{2+} channels	μ-opiate agonists, gabapentin, clonidine, tricyclic antidepressants, *δ-opiate agonists, adenosine agonists, $GABA_{A/B}$ agonists, nAChR agonists, CB2 agonists* ωConotoxin

NOTE: Drugs under development are shown in italics.

Costigan M, Woolf CJ. Pain: molecular mechanisms. J Pain 2000;1(suppl 1):35-44.

20 recent negative neuropathic pain trials (and there are many others[1])

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 PHN
Oxcarbazepine in painful DPN (2 trials)
Oxcarbazepine in lumbosacral radiculopathy
Pregabalin in painful HIV neuropathy
Pregabalin in lumbosacral radiculopathy
Propentofylline in PHN
Topiramate in painful DPN (3 trials)
Gabapentin extended-release in PHN
Pregabalin in painful DPN (4 trials)

[1]see Finnerup NB, et al. Pain 2010;150:573-581.

Why have so many recent analgesic trials been negative?

1. Some of these drugs may have limited or no efficacy.
2. Many of these recent results are actually false negatives.
   - ~ 50% of depression trials of approved antidepressants fail...
   - placebo group patients improved “too much.”
   - the optimal pain patients and pain phenotypes were not studied (“personalized pain medicine”).
   - temporal changes in characteristics of patients enrolling in trials.
   - temporal changes in types of sites conducting trials.

Regulatory Issues Related to the Development of Drugs to Treat Painful Peripheral Neuropathy

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Innovative Therapies for Peripheral Neuropathies
2012 FPN National Research Symposium
The Foundation for Peripheral Neuropathy
Chicago
March 15, 2012

Background

- Clinical studies, particularly efficacy trials, notoriously flawed for analgesic drug development
  - Frequent failed studies with drugs known to be effective
  - Extremely small treatment effects even when successful
  - Multiple causes, e.g.:
    - Large placebo effect
    - Missing data
    - Study design flaws
    - Study analysis flaws
    - Investigator quality
    - Frequent use of foreign sites

Background

- Although somewhere between 30 and 60 million people suffer from chronic pain in US
- And the dangers of treating acute pain with opioids, NSAIDS or acetaminophen are considerable
- Industry reluctant to put money into novel analgesic development with a low success rate of clinical trials

Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks

Home | Organization | Meetings | Resources | Partnership with FDA | Other Partners | IMMPACT | Contact Us

Agenda and Registration Information for 2nd ACTTION Scientific Workshop

The mission of ACTTION is to identify, prioritize, sponsor, coordinate, and promote innovative activities — with a special interest in optimizing clinical trials — that will expedite the discovery and development of improved analgesic, anesthetic, and addiction treatments for the benefit of the public health.

study assay sensitivity and efficiency.

The limitations of existing pain treatments are an international concern, and ACTTION is intended to have benefits that are international in scope. To represent the bridges that ACTTION is establishing among its diverse stakeholders, this website is illustrated with watermarks of two bridges that share the distinction of connecting different continents. Directly below is the First Bosphorus Bridge in Istanbul, Turkey, which connects Europe and Asia; on the Contact Us webpage is the Leifur Eiriksson Bridge in Iceland's Reykjanes peninsula, which spans a rift valley between the North American and European

ACTTION Board of Advisors

Daniel Carr, MD, Saltonstall Professor of Pain Research and Professor of

www.acttion.org

Current ACTTION activities, I

1. IMMPACT consensus meeting on "The Role of Biomarkers and Related Measures in the Development of Improved Analgesic Treatments" (June 2012).

2. ACTTION meeting on "Preclinical and Clinical Models and Methods for Accelerating Analgesic Drug Discovery and Development" (October 2012).

3. Development of pain-specific CDISC database standard for retrospective pooling and for prospective database creation and submission of analgesic trials.

4. Development of comprehensive registry of analgesic trials available from government and industry websites and other sources; ongoing publication bias analyses.

Current ACTTION activities, II

5. Systematic review and meta-analyses of safety reporting in analgesic trials, focusing on adherence to CONSORT recommendations; also assessment methods and approaches to data analysis and presentation.

6. Development of novel composite outcome measures for use in analgesic clinical trials, including: (1) pain and physical functioning; (2) pain and use of rescue analgesia; and (3) pain and adverse events (risk-benefit).

7. Statistical modeling to examine: (1) treatment of missing data; (2) parametric vs. non-parametric analysis methods; and (3) power and appropriateness of different analysis techniques, for example, landmark, time-weighted, and area under the curve.

Current ACTTION activities, III

8. Meta-regression analyses of study-level data from published and publicly-available clinical trials: (1) neuropathic pain; (2) OA; and (3) post-operative pain.
9. Analyses of patient-level pooled data from neuropathic pain, OA, and fibromyalgia trials made available by FDA and industry.
10. Development of definitions, classification system, and rating scales for evaluating misuse/abuse in analgesic trials (modeled after FDA-sponsored C-CASA and C-SSRS for evaluating suicidality in clinical trials).
11. Development of patient and staff training to increase assay sensitivity of pain ratings and other patient-reported outcomes; then proof-of-concept trial to test hypothesis that the training increases assay sensitivity.

An evidence-based approach to analgesic clinical trial design

1. Investigate relationships between the methodologic features of clinical trials and their "assay sensitivity" (i.e., *ability to distinguish efficacious treatments from placebo or less efficacious treatments*)

   - e.g., are certain patient characteristics associated with greater assay sensitivity?

2. Determine whether assay sensitivity can be increased by modifying these study features

   - e.g., possibly by reducing placebo group improvement

Patient factors

- Minimum pain duration
- Maximum pain duration
- Baseline diary compliance
- Minimum mean baseline pain intensity
- Maximum mean baseline pain intensity
- Baseline pain variability
- Baseline pain consistency
- History of treatment failure(s)
- Sources of patient referrals
- History of psychopathology

Study design factors

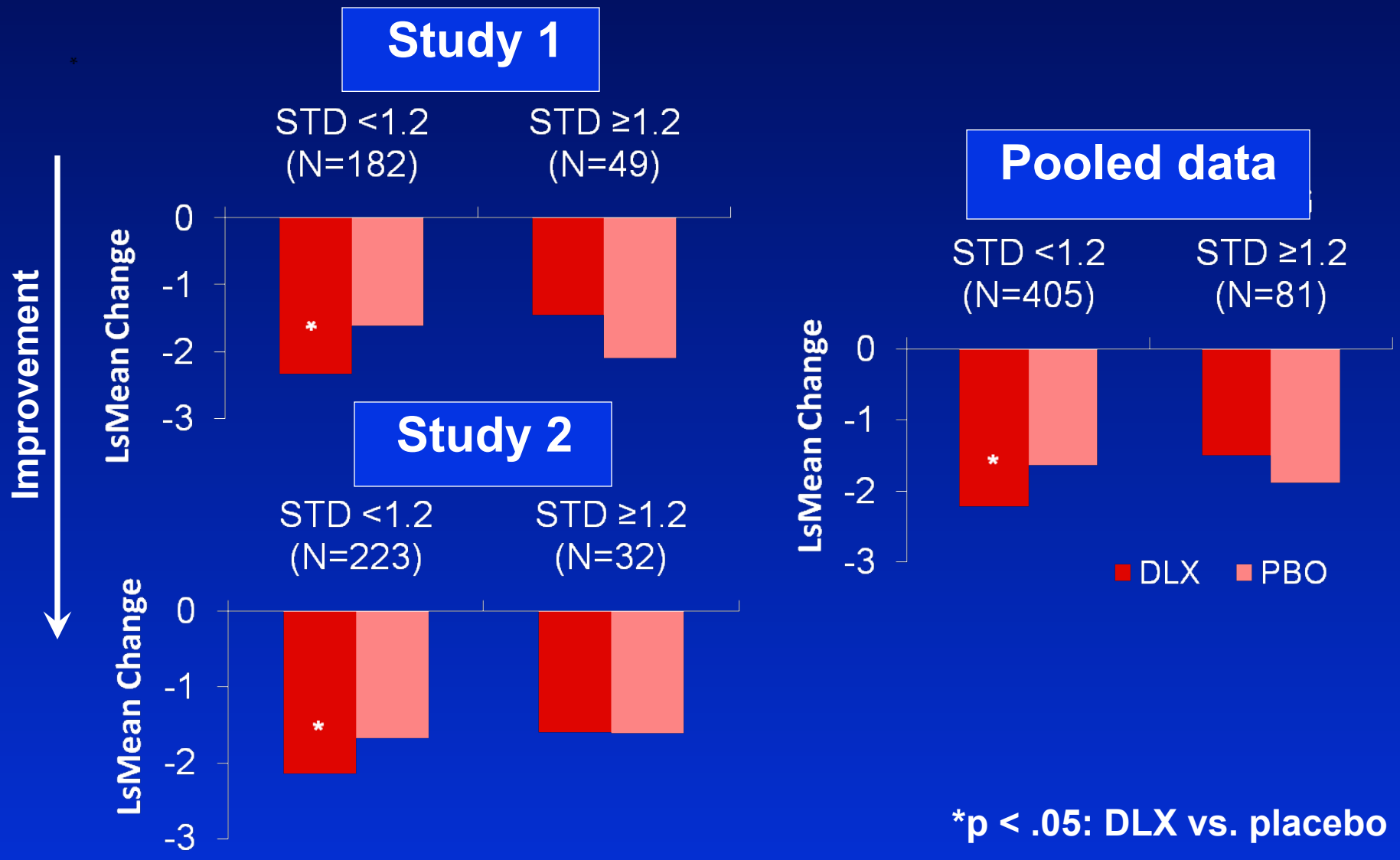
- Research design (e.g., parallel group vs. cross-over)
- Number of treatment arms
- Study duration
- Study quality
- Baseline period duration
- Titration period presence and duration
- Dosing strategy (e.g., flexible vs. fixed)
- Permitted use of rescue and/or concomitant analgesics
- Presence of active comparator
- Outcome measures
- Methods of data collection (e.g., paper vs. electronic)

Study site factors

- Sources of patient referrals
- Number of sites
- Site investigator and staff experience
- Site investigator and staff training
- Inclusion of patient training
- Methods for accelerating enrollment
- Geographic region

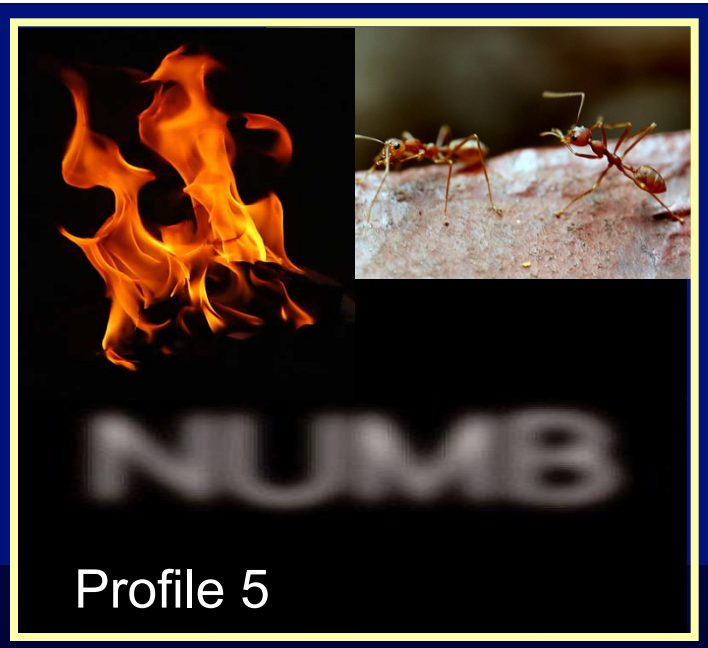
Can we improve the selection of patients for clinical trials?

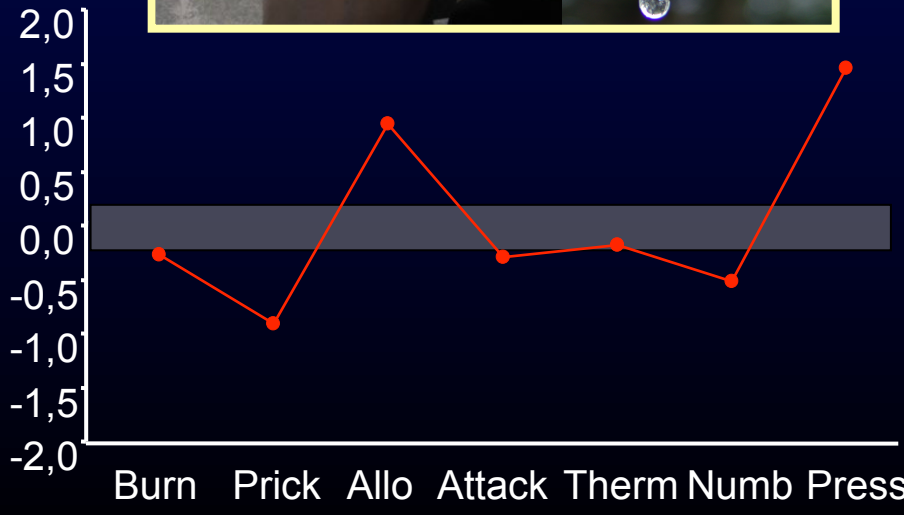
Variability in baseline pain daily diaries and treatment vs. placebo differences in OA

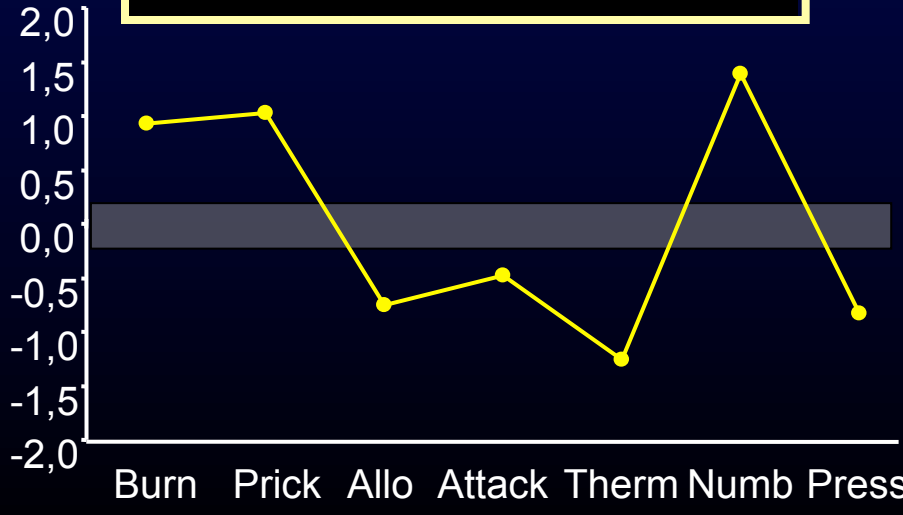


*p < .05: DLX vs. placebo

Sensory Profiles – Subgroups

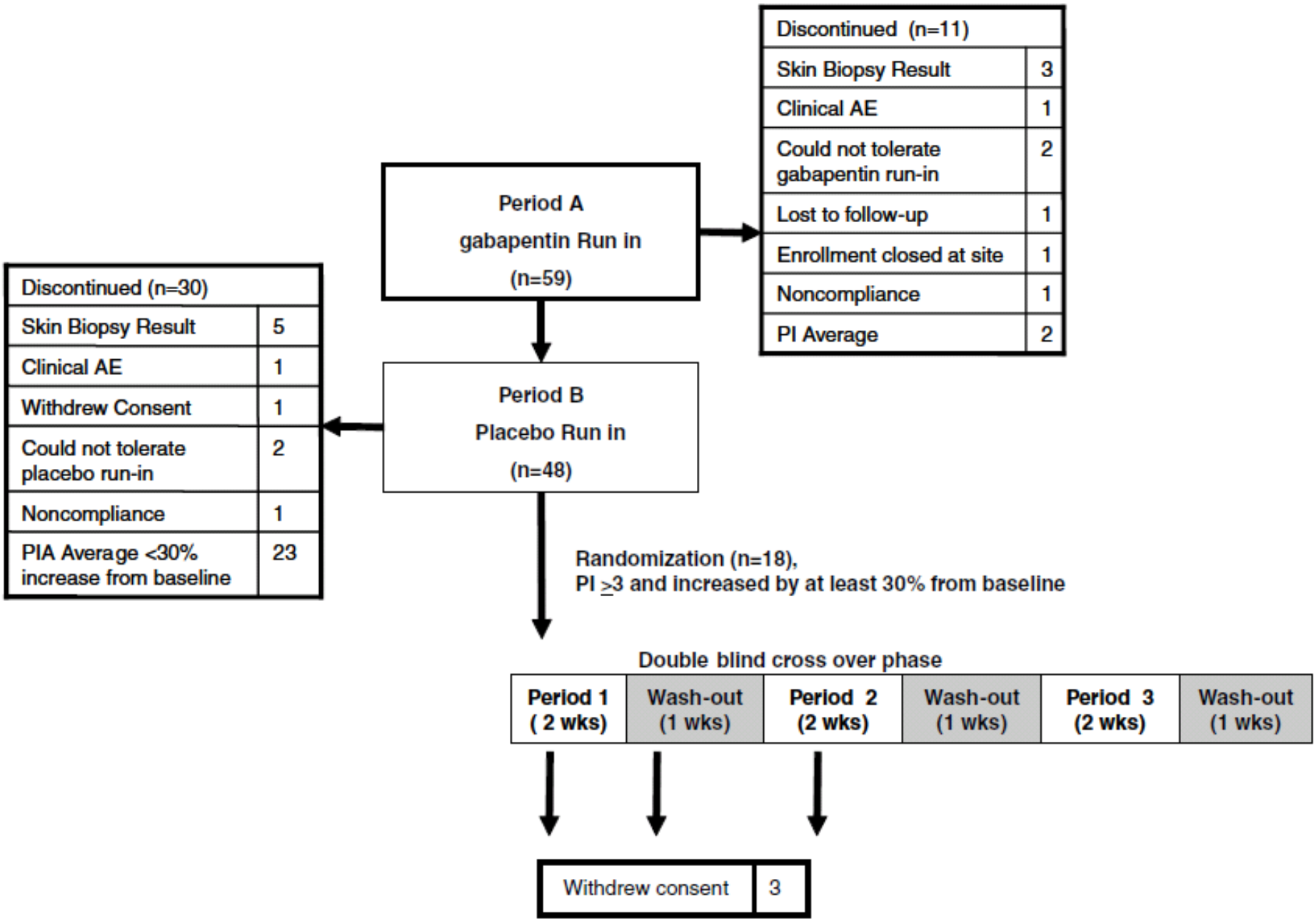


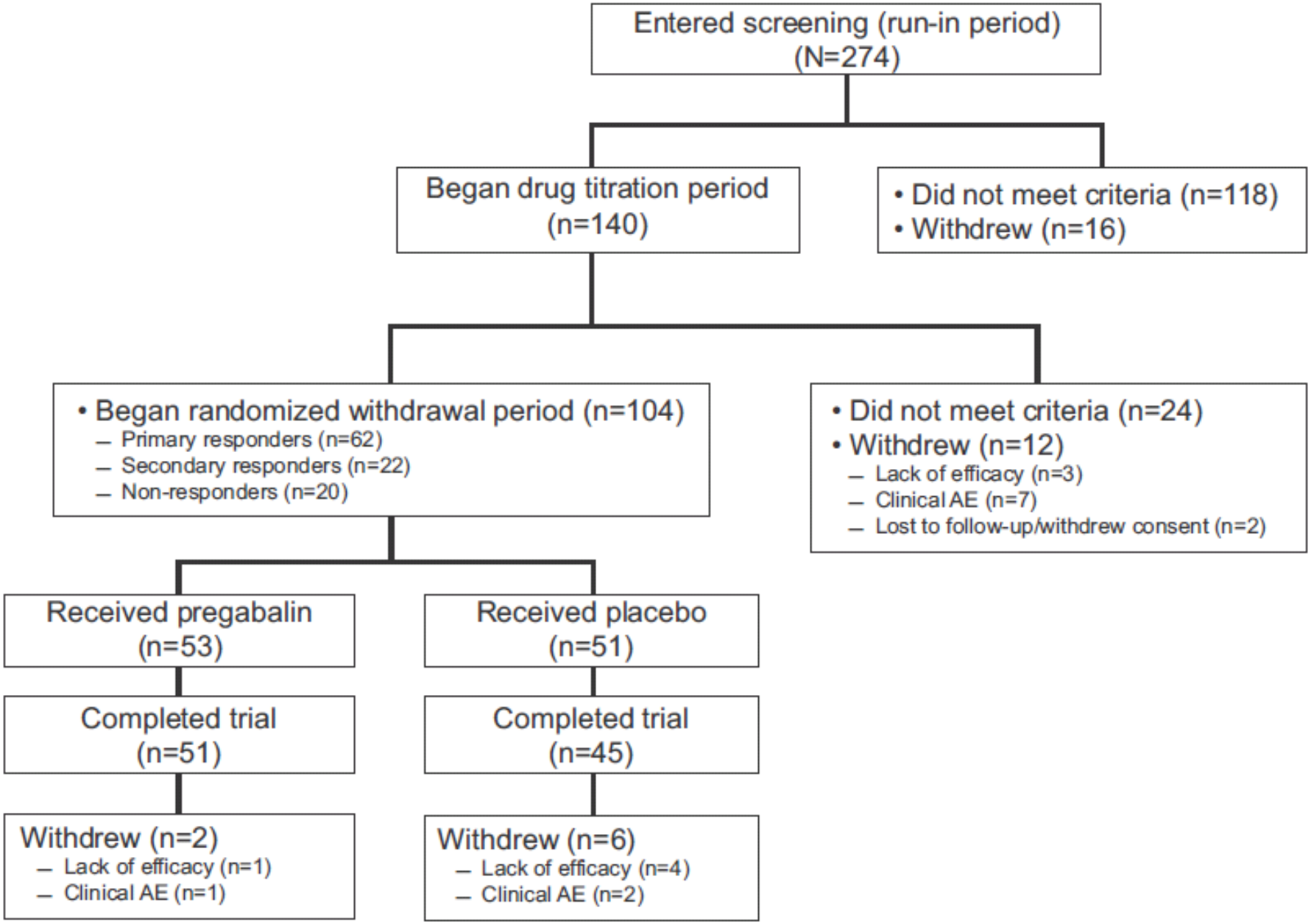




Baron R, et al. Pain 2009;146:34-40.

Can we improve clinical trial research designs and methods?


Period A
gabapentin Run in
(n=59)
Discontinued (n=11)
Skin Biopsy Result 3
Clinical AE 1
Could not tolerate gabapentin run-in 2
Lost to follow-up 1
Enrollment closed at site 1
Noncompliance 1
PI Average 2
Period B
Placebo Run in
(n=48)
Discontinued (n=30)
Skin Biopsy Result 5
Clinical AE 1
Withdrew Consent 1
Could not tolerate placebo run-in 2
Noncompliance 1
PIA Average <30% increase from baseline 23
Randomization (n=18),
PI ≥3 and increased by at least 30% from baseline
Double blind cross over phase
Period 1 (2 wks)
Wash-out (1 wks)
Period 2 (2 wks)
Wash-out (1 wks)
Period 3 (2 wks)
Wash-out (1 wks)
Withdrew consent 3


Entered screening (run-in period)
(N=274)
Began drug titration period
(n=140)
• Did not meet criteria (n=118)
• Withdrew (n=16)
• Began randomized withdrawal period (n=104)
– Primary responders (n=62)
– Secondary responders (n=22)
– Non-responders (n=20)
• Did not meet criteria (n=24)
• Withdrew (n=12)
– Lack of efficacy (n=3)
– Clinical AE (n=7)
– Lost to follow-up/withdrew consent (n=2)
Received pregabalin
(n=53)
Received placebo
(n=51)
Completed trial
(n=51)
Completed trial
(n=45)
Withdrew (n=2)
– Lack of efficacy (n=1)
– Clinical AE (n=1)
Withdrew (n=6)
– Lack of efficacy (n=4)
– Clinical AE (n=2)

“Both investigators and patients were blinded to the following information: entry criteria for patients’ pain intensity, baseline pain intensity, definition of responder groups, visit at which randomization occurred, treatment during the withdrawal phase, efficacy failure criteria, and computation rules and time windows in the IVRS system used to calculate the baseline intensity and pain response.”

Hewitt DJ, et al. Pain 2011;152:514-521.

And what can be done about clinical trial study sites?

FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

TRANSFORMING CLINICAL RESEARCH IN THE UNITED STATES

CHALLENGES AND OPPORTUNITIES

WORKSHOP SUMMARY

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

The IOM report describes the existence in psychiatry trials of "professional patients" — individuals who participate in multiple trials as a source of income and medication — noting the example of a 300 patient schizophrenia trial in which 30 subjects were found to have been randomized to the same study by multiple study sites.

Home » Healthcare » Health Information & Medical Research » Clinical Trials » How to Participate in More Than One Clinical Tria

Top 5 To Try

- How to Participate in Clinical Trials for Pay
- How to Participate in Depression Clinical Drug Trials
- How to Participate in Clinical Trials for Healthy Volunteers
- How to Design a Clinical Trial
- How to Manage Clinical Trials

Ads by Google

Top Depression Treatments

2011 Top (3) Depression Treatments Have Been Found. See Them Now ServiceMountain.com/Depre

Taking an Antidepressant?

Having persistent depression? New

How to Participate in More Than One Clinical Trial

By Breann Kanobi, eHow Contributor

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Clinical trials often involve taking prescription medicine.

Participants in clinical trials typically receive treatment for a medical condition. These trials divide participants into groups so each group tries a different medication with one group taking a placebo, or sugar pill. This placebo group acts as a control so the trial's organizers can see how a treatment compares with no treatment. Participants often collect a monetary reward for participation in these programs. If you wish to collect multiple rewards, you may be able to participate in multiple clinical trials, depending on the rules of the clinical trial.

Related Searches: Clinical CRF Medical Research Study

Instructions

Difficulty: Moderate

Concerns about the clinical trial enterprise have provided the impetus for a proposal made by Dr. Janet Woodcock that a clinical trial infrastructure should be developed in the US.

This infrastructure would provide a permanent network of sites, investigators, and staff with expertise and funding that would replace the ad hoc manner in which trials are now conducted.

ACTTION plans to start developing such a network for analgesic clinical trials.

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www.elsevier.com/locate/pain

Review and recommendations

Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations

Robert H. Dworkin [a,*], Dennis C. Turk [b], Sarah Peirce-Sandner [c], Laurie B. Burke [d], John T. Farrar [e], Ian Gilron [f], Mark P. Jensen [b], Nathaniel P. Katz [g,h], Srinivasa N. Raja [i], Bob A. Rappaport [d], Michael C. Rowbotham [j], Misha-Miroslav Backonja [k], Ralf Baron [l], Nicholas Bellamy [m], Zubin Bhagwagar [n], Ann Costello [d], Penney Cowan [o], Weikai Christopher Fang [p], Sharon Hertz [d], Gary W. Jay [q], Roderick Junor [r], Robert D. Kerns [s,t], Rosemary Kerwin [u], Ernest A. Kopecky [v], Dmitri Lissin [w], Richard Malamut [x], John D. Markman [c], Michael P. McDermott [c], Catherine Munera [y], Linda Porter [z], Christine Rauschkolb [aa], Andrew S.C. Rice [ab], Cristina Sampaio [ac], Vladimir Skljarevski [ad], Kenneth Sommerville [ae], Brett R. Stacey [af], Ilona Steigerwald [ag], Jeffrey Tobias [ah], Ann Marie Trentacosti [d], Ajay D. Wasan [ai], George A. Wells [aj], Jim Williams [ak], James Witter [x], Dan Ziegler [al]