The ACTTION public-private partnership: what is the FDA doing to accelerate the development of better analgesics?

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The mission of ACTION 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 treatments for the benefit of the public health.
Regulatory Issues Related to the Development of Drugs to Treat Painful Peripheral Neuropathy

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Innovative Therapies for Peripheral Neuropathies
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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
Objectives

• Primary objective: develop novel analgesic drugs products
  – “broad spectrum”
  – Targeted
  – Additive and/or synergistic
  – And with less toxicity

• By exploring the flaws in current analgesic clinical trial designs

• Testing novel designs and analyses

• Standardizing data presentation to allow for more efficient exploration and analysis
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. Meta-regression analyses of study-level data from published and otherwise publicly-available analgesic clinical trials: (1) neuropathic pain; (2) osteoarthritis; and (3) acute post-operative pain.

4. Analyses of patient-level pooled data from neuropathic pain trials; also osteoarthritis and fibromyalgia trials (in collaboration with Europain).
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
<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Study design factors</th>
<th>Study site factors</th>
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<tbody>
<tr>
<td>• Minimum pain duration</td>
<td>• Research design (e.g., parallel group vs. cross-over)</td>
<td>• Sources of patient referrals</td>
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<tr>
<td>• Maximum pain duration</td>
<td>• Number of treatment arms</td>
<td>• Number of sites</td>
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<td>• Baseline diary compliance</td>
<td>• Study duration</td>
<td>• Site investigator and staff experience</td>
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<td>• Minimum mean baseline pain intensity</td>
<td>• Study quality</td>
<td>• Site investigator and staff training</td>
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<tr>
<td>• Maximum mean baseline pain intensity</td>
<td>• Baseline period duration</td>
<td>• Inclusion of patient training</td>
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<td>• Baseline pain variability</td>
<td>• Titration period presence and duration</td>
<td>• Methods for accelerating enrollment</td>
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<td>• Baseline pain consistency</td>
<td>• Dosing strategy (e.g., flexible vs. fixed)</td>
<td>• Geographic region</td>
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<td>• History of treatment failure(s)</td>
<td>• Permitted use of rescue and/or concomitant analgesics</td>
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<td>• Sources of patient referrals</td>
<td>• Presence of active comparator</td>
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<td>• History of psychopathology</td>
<td>• Outcome measures</td>
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<td>• Methods of data collection (e.g., paper vs. electronic)</td>
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Current ACTTION activities, II

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

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

7. 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.

8. Development of definitions, classification system, and rating scales for evaluating misuse/abuse in studies of analgesic drugs (modeled after FDA-sponsored C-CASA and C-SSRS for evaluating suicidality in clinical trials).
Current ACTTION activities, III

9. Development of patient and staff training programs to increase assay sensitivity of pain ratings and other patient-reported outcomes, followed by proof-of-concept trial to test hypothesis that the training increases assay sensitivity.

10. 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).

11. Statistical modeling to examine: (1) treatment of missing data; (2) parametric vs. non-parametric methods of analysis; and (3) power and appropriateness of different analysis techniques, for example, landmark, time-weighted, and area under the curve.
Can we improve the selection of patients for clinical trials?
Variability in baseline pain daily diaries and treatment vs. placebo differences in OA

**Study 1**
- STD <1.2 (N=182)
- STD ≥1.2 (N=49)

- *p < .05: DLX vs. placebo

**Study 2**
- STD <1.2 (N=223)
- STD ≥1.2 (N=32)

**Pooled data**
- STD <1.2 (N=405)
- STD ≥1.2 (N=81)

* *p < .05: DLX vs. placebo*
Can we improve clinical trial research designs and methods?
“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.”

And what can be done about clinical trial study sites?
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.
Concerns about the clinical trial enterprise have provided the impetus for a proposal made by Dr. Janet Woodcock in the IOM report that the US should develop a clinical trial infrastructure. This infrastructure would provide a permanent network of resources (e.g., sites, investigators, staff), expertise, and funding that would replace the ad hoc manner in which clinical trials are currently conducted.
Review and recommendations

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