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Active Controls in Antipsychotic Trials
Why Have Them?

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Disclaimer

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Assessment of Efficacy

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Distinguishing Negative Trials from Failed Trials

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Assay Sensitivity

Assay sensitivity[1]

- **The ability of a trial to distinguish an effective treatment from a less effective or ineffective intervention**
- **Without assay sensitivity, a trial is not internally valid and is not capable of comparing the efficacy of two interventions**

1-Wikipedia

Assay sensitivity

Lack of assay sensitivity has different implications for:

- **Superiority trials**
  (trials intended to show a difference greater than zero between interventions)

→ ***fail to show that the test intervention is superior and will fail to lead to a conclusion of efficacy***

- **Non-inferiority trials**
  (trials to rule out some margin of inferiority between a test and control)

→ ***may find an ineffective intervention to be non-inferior and could lead to an erroneous conclusion of efficacy***

Assay sensitivity

- **When two interventions within a trial are shown to have different efficacy that finding itself directly demonstrates that the trial had assay sensitivity (assuming the finding is not related to random or systematic error)**
- **Scientific debate regarding use of assay sensitivity as an inclusion criterion for meta-analysis (Klein[2] v. Gelfand[3])**

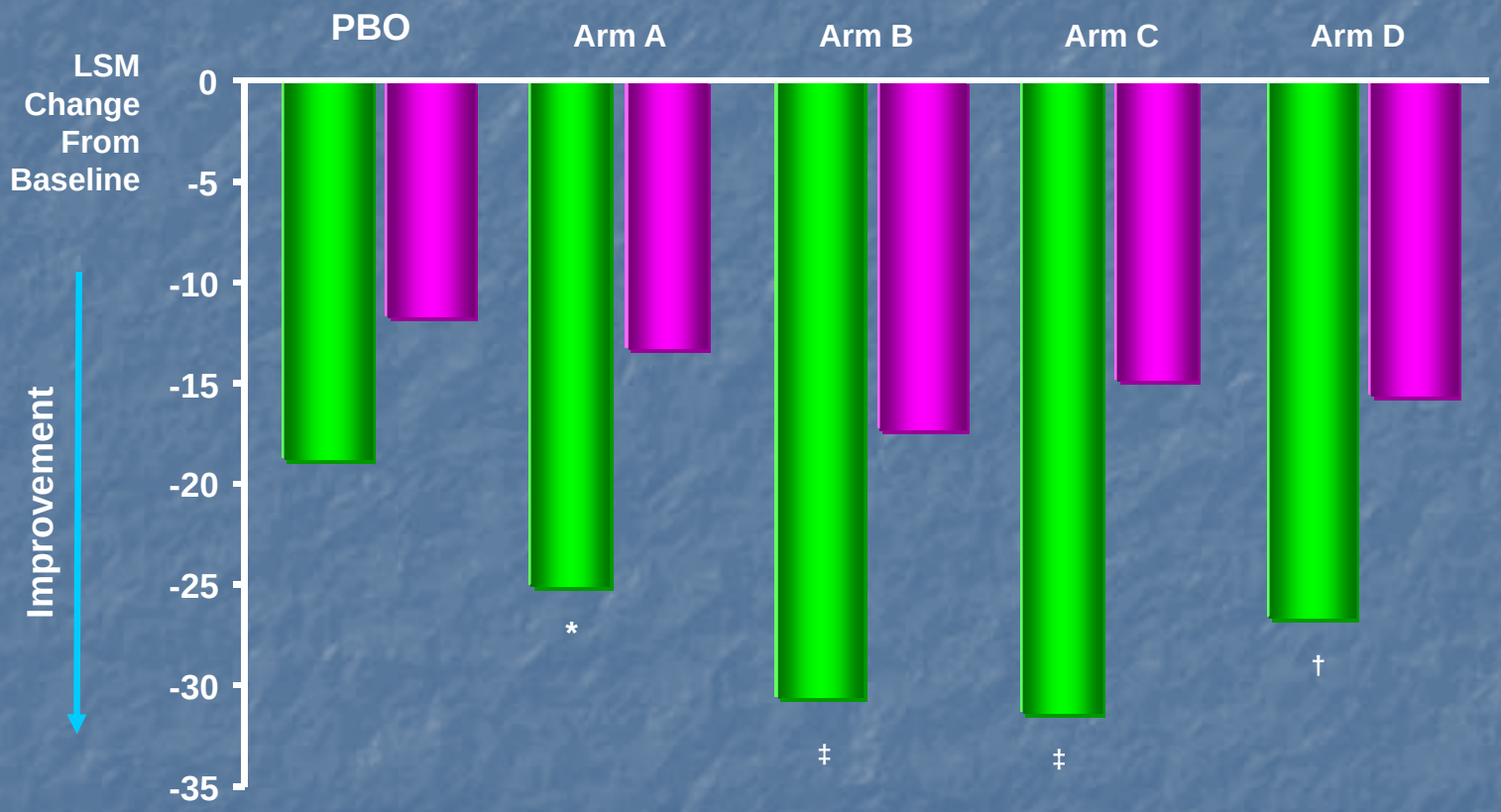
2- Am J Psychiatry. 2000 Aug;157(8):1204-11
3- Statistics in medicine 2006, vol. 25, nº6, pp. 943-955

Assay sensitivity

- **Need for active control to assess assay sensitivity particularly important in psychiatry clinical trials with a high failure rate:**
  - **Historically in trials of antidepressants**[4]
  - **More recently a possible rising failure rate in trials of antipsychotics**[5]
  - **Recent mounting evidence of attenuated drug arm effect**
    (more data at upcoming ISCDD meeting)

4- Temple, Ellenberg, Ann Intern Med. 2000;133:455-463
5- Kemp et al Schizophrenia Bulletin, doi:10.1093/schbul/sbn110

PANSS Total Score: At Day 42
Comparison of Two Studies



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Assessment of Safety
Risk : Benefit Assessment?

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State Of Play Up To Recently

There is no provision in FDA regulations for a policy that would permit new products to be marketed only if they showed some advantage over existing treatments, no matter how large the pool of existing treatments might be

Temple, Ellenberg, Ann Intern Med. 2000;133:464-470

Examples of Therapeutic Advances in Which New Treatment Was No More Effective Than Established Treatment

Drug Class	Existing Drug	New Agent	Advance
Antidepressants	Tricyclic antidepressants	SSRIs and others	better accepted side effects
Antipsychotic drugs	Phenothiazines, butyrophenones	Risperidone, olanzapine, quetiapine	Decreased extrapyramidal effects
Antihistamines	Sedating antihistamines	Nonsedating antihistamines	Lack of sedation
Antianginals	Organic nitrates	ß-Blockers, calcium-channel blockers	Lack of tolerance
Anti-inflammatory drugs	Nonselective NSAIDs	COX-2–selective NSAIDs	Potential for decreased GI bleeding
Antihypertensive drugs	Diuretics, reserpine	Angiotensin-converting enzyme inhibitors, calcium-channel blockers	Elimination of important side effects (hypokalemia and depression)

Temple, Ellenberg, Ann Intern Med. 2000;133:464-470

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Have Recent Applications Identified New Risk: Benefit Challenges?