Not All that Glitters is Gold…

A Critical Interpretation of Drug Trials in Epilepsy

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Practicing Evidence-Based Medicine: Sources of Evidence

- Retrospective studies - case observations
- Prospective uncontrolled trials
- Randomized controlled trials (RCTs)
- (Metanalysis of RCTs)

Outline

- Value and limitations of uncontrolled AED studies*
- RCTs - theory and practice
- The hidden world

*>95% of AED studies published in peer review journals (2000-2016)

Problems with Uncontrolled Trials "Objective" is not the Same as "Unbiased"!

Responder Rates* to Lamotrigine in LGS Trials

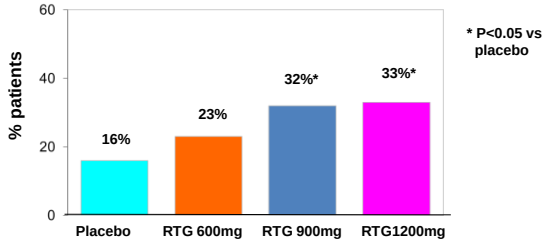
Timmings et al (1992)	uncontrolled	91%
Schlumberger et al (1994)	uncontrolled	60%
Suarez et al (1995)	uncontrolled	60%
Buchanan et al (1996)	uncontrolled	57%
Donaldson et al (1997)	uncontrolled	53%
Farrell et al (1997)	uncontrolled	73%
Yen et al (1997)	uncontrolled	80%
Motte (1997)	double-blind	33%**

* patients showing at least 50% reduction in drop attacks vs baseline
** 16% responder rate in placebo group

LGS = Lennox Gastaut syndrome

Perucca and Wiebe, Epilepsia Open 2015 (in press)

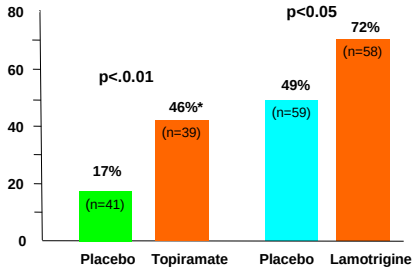
Double-Blind Placebo-Controlled Add-on Trial of Retigabine (RTG) in Adults with Focal Seizures: 50% Responder Rates (n=396, ITT analysis))



Porter et al., Neurology 2007;68:1197-1204

Add-on Trials in Refractory Epilepsy: Can Historical Placebo Rates be Used to Estimate an AED's Efficacy?

Responder Rates in Primary Generalized Tonic-Clonic Seizures



Biton et al. Neurology 1999; 52: 1330-7. Biton et al. Neurology 2005; 65:1637-43

"The best way to improve the outcome of a therapeutic trial is to leave out the controls"

Hugo Muench

Usefulness of Uncontrolled Trials

- To assess pharmacokinetics and drug interactions
- To explore, and generate signals about potential efficacy (and tolerability) in specific syndromes, prior to conduction of controlled studies
- To provide (misleading) supportive 'evidence' for drug promotion (seeding trials)

Memorandum (from marketing dept to sales reps)

"Make no mistake: The Ypertin study is the single most important sales initiative for 1993. Phase I provides 2500 physicians with the opportunity to observed in their patients…blood pressure control…by Ypertin. If at least 20,000 of the 25,000 patients involved in the study remain on Ypertin it could mean up to a $ 10,000,000 boost in sales. In phase II, this figure could double.."

Kessler et al New Engl J Med 1994;331:1350-3.

Some Common Justifications for Conducting Uncontrolled Trials

- They are easier to conduct (true, but not a good reason to do bad science)
- They are the only way to mimick clinical practice (wrong – randomized trials can mimic clinical practice equally well)
- They are the only option in rare syndromes, for which it is impossible to find enough patients for a RCT (wrong – randomized trials can be effectively conducted with few patients)

Cornu et al. Orphanet Journal of Rare Diseases 2013, 8:48
http://www.ojrd.com/content/8/1/48

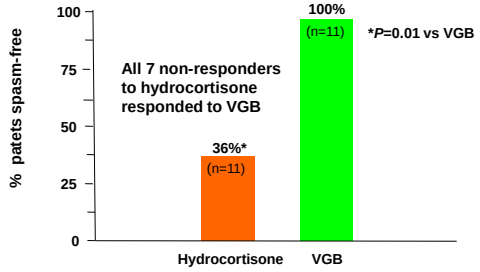
ORPHANET JOURNAL OF RARE DISEASES

REVIEW Open Access

Experimental designs for small randomised clinical trials: an algorithm for choice

Catherine Cornu[1,2,3*], Behrouz Kassai[1,2,3], Roland Fisch[4], Catherine Chiron[5], Corinne Alberti[6,7,8], Renzo Guerrini[9], Anna Rosati[9], Gerard Pons[10], Harm Tiddens[11], Sylvie Chabaud[12], Daan Caudri[11], Clément Ballot[3], Polina Kurbatova[3], Anne-Charlotte Castellan[3], Agathe Bajard[12], Patrice Nony[2,3] and the CRESim & Epi-CRESim Project Groups

RCT of Steroids vs Vigabatrin (VGB) in West Syndrome Associated with Tuberous Sclerosis



Chiron et al. Epilepsy Research 1997; 26: 389-95.

Are Randomized Controlled Trials (RCTs) the Answer to All Questions?

RCTs are by far the best source of evidence, but..

- They are not suitable to address all therapeutic questions
- They control for several sources of bias – but not for all!
- They are are dependent on methodological constraints
- Need to be interpreted critically!!!

Most Randomized Trials of AEDs are Conducted to Obtain a Marketing License

To obtain a marketing license for add-on use of a new AED in the U.S., Europe, and Thailand, you need to show that the new AED is:

1. Better than nothing
2. At least as good as an already marketed AED
3. Better than an already marketed AED

Regulatory Trials

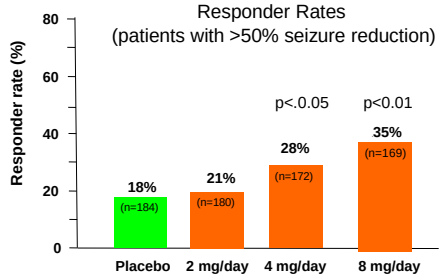
Advantages

- Usually double-blind RCTs
- Often placebo-controlled
- Standardized methodology
- High scientific standards

Disadvantages

- Often "artificial" setting
- Patients, dosing, and trial duration may not reflect optimal clinical use
- Question addressed differs from clinician's needs

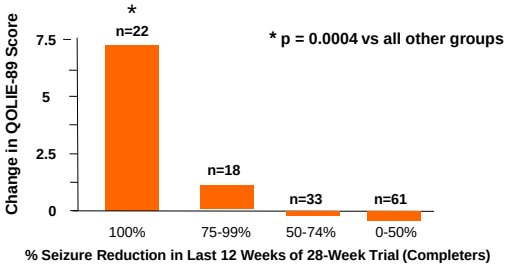
Perampanel vs Placebo as Adjunctive Treatment in Adults with Pharmacoresistant Focal Seizures



Krauss et al. Neurology 2012; 81:1408-1415

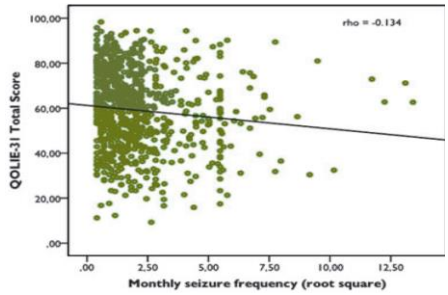
How Does a Reduction in Seizure Frequency Impact on Quality of Life?

Lessons from a Vigabatrin Randomized Add-on Trial



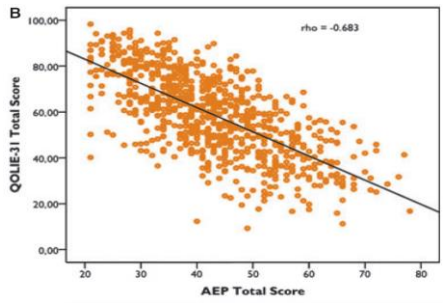
Birbeck et al. Epilepsia 2002;43:355-8.

Seizure Frequency vs Quality of Life in 809 Patients with Refractory Epilepsy in Italy



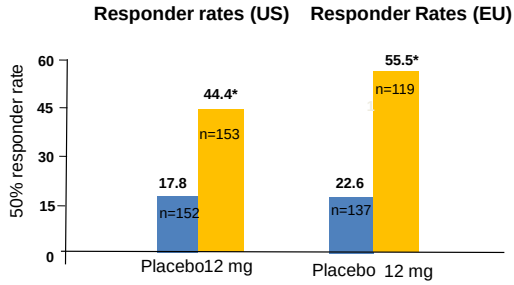
Luoni et al, SOPHIE Study Group, Epilepsia; 2011;52: 2181-91

Adverse Drug Effects vs Quality of Life in 809 Patients with Refractory Epilepsy in Italy



Luoni et al, SOPHIE Study Group, Epilepsia; 2011;52: 2181-91

Responder Rates: Not as Simple as it Looks! Perampanel 12 mg vs Placebo (ITT analysis)

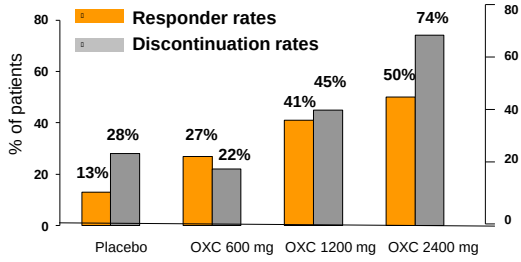


*P<0.01 vs placebo

French et al, Neurology 2010; 75:1817-1824

Responder Rates as a Function of Dose (2)

Randomized Add-on Trial of Oxcarbazepine (OXC) in Focal Seizures



•All OXC dosages: p<0.001 vs placebo

Barcs et al, Epilepsia 2000;41:1597-607

A Systematic Review of Placebo-Controlled Add-on Trials of Any AED in Refractory Focal Epilepsy

Out of a total of 63 RCTs identified (1967-2009), how many reported responder rates in completers?

- < 5%
- 5-20%
- 21-50%
- >50%

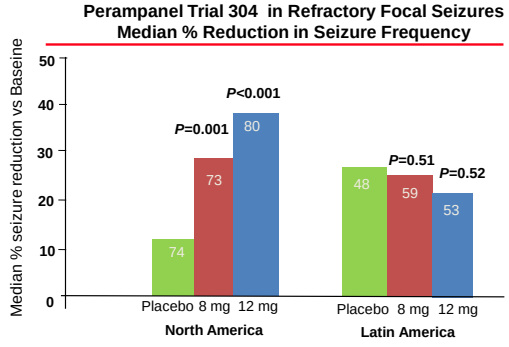
Rheims et al, Epilepsia 2011:52:219-233

Randomized Does Not Mean Unbiased!

Common Bias that Could Modify Outcomes in a RCT

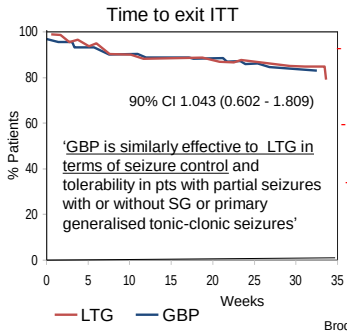
- Number and characteristics of study sites
- Eligibility criteria (e.g., inclusion of patients with primary generalised tonic-clonic seizures when carbamazepine is a comparator)
- Dosages of products being compared
- Formulations, titration and dosing intervals
- Duration of follow-up
- Data analysis and endpoints

Does It Matter which Centers, or Where?



French et al, Neurology 2012; 79:589-96

Getting Population & Trial Duration Wrong
Gabapentin vs Lamotrigine in Newl-Onset Epilepsy



- Pts with 2 sz in the previous 12 months or 1 sz plus positive EEG or imaging
- 24 wk maintenance, with dose adjustment possible
- pts with PGTCS who had to exit: 0/27 LTG, 5/31 GBP

Brodie et al, Epilepsia 43:993-1000, 2002

Comparative tolerability of new and old AEDs in RCTs in patients with newly diagnosed epilepsy

Trial	N	New AED better tolerated?	Reference
LTG vs CBZ	260	Yes	Brodie *et al. Lancet* 1995;**345**:476–9
LTG vs CBZ	343	Yes	Reunanen *et al. Epilepsy Res* 1996;**23**:149–55
LTG vs CBZ	150	Yes	Brodie *et al. Epilepsy Res* 1999;**37**:81–7 §
LTG vs PHT	181	Yes	Steiner *et al. Epilepsia* 1999;**40**:601–7
LTG vs VPA/CBZ	239	Yes (vs CBZ)	Steinhoff *et al. Seizure* 2005;**14**:597–605
LTG vs CBZ/GBP	593	Yes	Rowan *et al. Neurology* 2005;**64**:1868–73 §
LTG vs CBZ	184	Yes	Saetre *et al. Epilepsia* 2007;**48**:1292–302 §
LTG vs CBZ	756	Yes	Marson *et al. Lancet* 2007;**369**:1000–15
LTG vs VPA	475	Yes	Marson *et al. Lancet* 2007;**369**:1016–29
VGB vs CBZ	100	Yes	Kalviainen *et al. Arch Neurol* 1995;**52**:989–96
VGB vs CBZ	58	Yes	Tanganelli & Regesta *Epilepsy Res* 1996;**25**:257–62
VGB vs CBZ	459	Yes	Chadwick *et al. Lancet* 1999;**354**:13–9

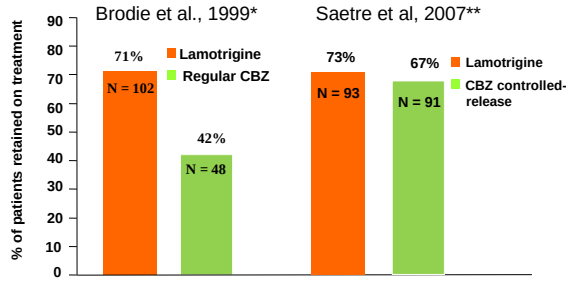
§ Trials in elderly patients

Comparative tolerability of new and old AEDs in RCTs in patients with newly diagnosed epilepsy

Trial	N	New AED better tolerated?	Reference
OXC vs CBZ	235	Yes	Dam *et al. Epilepsy Res* 1989;**3**:70-6.
OXC vs VPA	249	No	Christe *et al, Epilepsy Res.* 1997;**26**:451-60.
OXC vs PHT	287	Yes	Bill *et al. Epilepsy Res* 1997;**27**:195–204*
OXC vs CBZ	588	No	Marson *et al. Lancet* 2007;**369:**1000–15
GBP vs CBZ	292	Yes	Chadwick *et al. Neurology* 1998;**51**:1282–8
GBP vs CBZ/GBP	593	Yes	Rowan *et al. Neurology* 2005;**64**:1868–73 §
GBP vs CBZ	754	Yes	Marson *et al. Lancet* 2007;**369:**1000–15
TPM vs CBZ/VPA	613	No	Privitera *et al. Acta Neurol Scand* 2003;**107**:165–75
TPM vs CBZ	752	No	Marson *et al. Lancet* 2007;**369:**1000–15
TPM vs VPA	476	No	Marson *et al. Lancet* 2007;**369:**1016–29
LEV vs CBZ	579	No	Brodie *et al. Neurology* 2007;**68**:402–8
ZNS vs CBZ	583	No	Baulac et al, *Lancet Neurol.* 2012;**11**:579-88

*Pediatric trial; § Trial in elderly patients

What Difference can a Formulation Make?
Treatment Outcomes in RCTs of Epilepsy in the Elderly



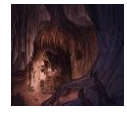
* 20 wk trial, Epilepsy Res. 1999;37:81-87 ** 40 wk trial, Epilepsia 2007;48:1292-1302
Dosing and titration schemes were identical in both trials

Quality of Randomized Trials in New Onset Epilepsy
Rating by the ILAE Criteria

Seizure type	N. of studies	Class I	Class II	Class III
Focal, adults	**39**	4	1	34
Focal, children	**20**	1	0	19
Focal, elderly	**5**	1	1	3
GTCS, adults	**29**	0	0	29
GTCS, children	**14**	0	0	14
Absence, children	**7**	1	0	6
BECTS	**3**	0	0	3
JME	**1**	0	0	1

Glauser et al, Epilepsia 2013;54:551-63

The Hidden World



- Incomplete data reporting
- Bias in data reporting
- Selective publication
- Ghost authorship

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use

S. Swaroop Vedula, M.D., M.P.H., Lisa Bero, Ph.D., Roberta W. Scherer, Ph.D., and Kay Dickersin, Ph.D.

N Engl J Med 2009;361:1963-71.

RESULTS

We identified 20 clinical trials for which internal documents were available from Pfizer and Parke-Davis; of these trials, 12 were reported in publications. For 8 of the 12 reported trials, the primary outcome defined in the published report differed from that described in the protocol. Sources of disagreement included the introduction of a new primary outcome (in the case of 6 trials), failure to distinguish between primary and secondary outcomes (2 trials), relegation of primary outcomes to secondary outcomes (2 trials), and failure to report one or more protocol-defined primary outcomes (5 trials). Trials that presented findings that were not significant ($P \geq 0.05$) for the protocol-defined primary outcome in the internal documents either were not reported in full or were reported with a changed primary outcome. The primary outcome was changed in the case of 5 of 8 published trials for which statistically significant differences favoring gabapentin were reported. Of the 21 primary outcomes described in the protocols of the published trials, 6 were not reported at all and 4 were reported as secondary outcomes. Of 28 primary outcomes described in the published reports, 12 were newly introduced.

N Engl J Med 2009;361:1963-71.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

N ENGL J MED 358;3 WWW.NEJM.ORG JANUARY 17, 2008

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

RESULTS

Among 74 FDA-registered studies, 31%, accounting for 3449 study participants, were not published. Whether and how the studies were published were associated with the study outcome. A total of 37 studies viewed by the FDA as having positive results were published; 1 study viewed as positive was not published. Studies viewed by the FDA as having negative or questionable results were, with 3 exceptions, either not published (22 studies) or published in a way that, in our opinion, conveyed a positive outcome (11 studies). According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive. Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11 to 69% for individual drugs and was 32% overall.

N ENGL J MED 358;3 WWW.NEJM.ORG JANUARY 17, 2008

PLoS Biology | www.plosbiology.org March 2010 | Volume 8 | Issue 3 | e1000344

OPEN ACCESS Freely available online PLOS BIOLOGY

Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy

Emily S. Sena[1,2,3], H. Bart van der Worp[4], Philip M. W. Bath[5], David W. Howells[2,3], Malcolm R. Macleod[1,6]*

1 Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom, 2 National Stroke Research Institute, Austin Health, University of Melbourne, Melbourne, Victoria, Australia, 3 Department of Medicine, Austin Health, University of Melbourne, Melbourne, Victoria, Australia, 4 Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Center, Utrecht, The Netherlands, 5 Stroke Trials Unit, University of Nottingham, Nottingham, England, United Kingdom, 6 Department of Neurology, NHS Forth Valley, Stirling, Scotland, United Kingdom

How ghost-writing threatens the credibility of medical knowledge and medical journals

Virginia Barbour

OPEN ACCESS Freely available online PLOS MEDICINE

Ghost Authorship in Industry-Initiated Randomised Trials

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1 Nordic Cochrane Centre, Copenhagen, Denmark, 2 Centre for Statistics in Medicine, Oxford, United Kingdom, 3 Department of Medicine, University of Toronto, Canada

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Competing Interests: The authors have declared that no competing interests exist.

Academic Editor: Liz Wager, United Kingdom

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ABSTRACT

Background

Ghost authorship, the failure to name, as an author, an individual who has made substantial contributions to an article, may result in lack of accountability. The prevalence and nature of ghost authorship in industry-initiated randomised trials is not known.

Methods and Findings

We conducted a cohort study comparing protocols and corresponding publications for industry-initiated trials approved by the Scientific-Ethical Committees for Copenhagen and Frederiksberg in 1994–1995. We defined ghost authorship as present if individuals who wrote the trial protocol, performed the statistical analyses, or wrote the manuscript, were not listed as authors of the publication, or as members of a study group or writing committee, or in an acknowledgment. We identified 44 industry-initiated trials. We did not find any trial protocol or publication that stated explicitly that the clinical study report or the manuscript was to be written or was written by the clinical investigators, and none of the protocols stated that clinical investigators were to be involved with data analysis. We found evidence of ghost authorship for 33 trials (75%; 95% confidence interval 60%–87%). The prevalence of ghost authorship was increased to 91% (40 of 44 articles; 95% confidence interval 78%–98%) when we included cases where a person qualifying for authorship was acknowledged rather than appearing as an author. In 31 trials, the ghost authors we identified were statisticians. It is likely that we have overlooked some ghost authors, as we had very limited information to identify the possible omission of other individuals who would have qualified as authors.

Ghost Authorship in Industry-Sponsored Drug Trials

- Analysis of 44 consecutive trials selected with conservative criteria among those submitted to Ethics Committees in Copenhagen
- Evidence of ghost authorship was found for 33 trials (75%)
- Ghost authorship increased to 40 trials (91%) when including cases where a person who should have been a primary author was only cited in the acknowledgments

Gotzsche et al, Plos Medicine 2007; 4:e19

Conclusions

- Clinical trials are the best source of evidence on which to base clinical decisions
- However, methodology must be scrutinized carefully, and results must be interpreted critically - the devil is in the detail!