Anti-epileptic drug harms: issues for meta-analysis

Catrin Tudur Smith

[1]*North West Hub for Trials Methodology Research*

Arif Shukralla[2], Sarah Donegan[1], Karla Hemming[3], Graham A. Powell[2], Paula Williamson[1], Anthony Marson[2]

[1]*North West Hub for Trials Methodology Research, Department of Biostatistics, University of Liverpool*

[2]*Clinical and Molecular Pharmacology, University of Liverpool*

[3] Public Health, Epidemiology and Biostatistics, *University of Birmingham*

Outline

- Quality of reporting of harms data
- Issues for evidence synthesis
- Can we borrow strength from other indications?

Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT Statement

John P.A. Ioannidis, MD; Stephen J.W. Evans, MSc; Peter C. Gøtzsche, MD, DrMedSci; Robert T. O'Neill, PhD; Douglas G. Altman, DSc; Kenneth Schulz, PhD; and David Moher, PhD, for the CONSORT Group*

In response to overwhelming evidence and the consequences of poor-quality reporting of randomized, controlled trials (RCTs), many medical journals and editorial groups have now endorsed the CONSORT (Consolidated Standards of Reporting Trials) statement, a 22-item checklist and flow diagram. Because CONSORT primarily aimed at improving the quality of reporting of efficacy, only 1 checklist item specifically addressed the reporting of safety.

Considerable evidence suggests that reporting of harms-related data from RCTs also needs improvement. Members of the CONSORT Group, including journal editors and scientists, met in Montebello, Quebec, Canada, in May 2003 to address this problem. The result is the following document: the standard CONSORT checklist with 10 new recommendations about reporting harms-related issues, accompanying explanation, and examples to highlight specific aspects of proper reporting.

We hope that this document, in conjunction with other CONSORT-related materials (www.consort-statement.org), will help authors improve their reporting of harms-related data from RCTs. Better reporting will help readers critically appraise and interpret trial results. Journals can support this goal by revising Instructions to Authors so that they refer authors to this document.

Ann Intern Med. 2004;141:781-788. www.annals.org

For author affiliations, see end of text.

For definitions of terms, see Glossary.

*For a list of members of the CONSORT Group, see Appendix 1, available at www.annals.org.

Assessing quality of reporting in anti-epileptic drug RCTs

- MEDLINE, Cochrane Library and Epilepsy Group trials register using search terms ‘‘epilepsy’’, ‘‘antiepileptic drug’’ and ‘‘seizure’’

- Inclusion criteria:
  - RCT published between January 1999 and December 2008
  - RCT comparing AEDs
  - patient population with epilepsy
  - RCT published in English
- Exclusion criteria:
  - RCTs assessing surgical interventions and vagus nerve stimulation

Title, abstract, introduction, discussion

Item	CONSORT item	% of trials meeting the criteria
1	Harms in title or abstract	87.5
2	Harms in introduction	74.3
21	Discusses prior AE data	67.8
22	Discussion is balanced	61.2
23	Discusses limitations	40.8

Methods

Item	CONSORT item	% of trials meeting the criteria
3	Definition of AE	36.2
4	All or selected sample	31.6
5	Treatment Emergent AE	46.7
6	Validated instrument	15.8
7	Validated dictionary	21.7
8	Mode of AE Collection	56.6
9	Timing of AE	76.3
10	Details of Attribution	33.3
11	Details of presentation and analysis	35.5
12	Handling of recurrent AE	7.2

Results

Item	CONSORT item	% of trials meeting the criteria
13	Early or late withdrawals	71.0
14	Serious AEs or death	72.3
15	Provide denominators for AEs	78.3
16	Provide definitions used for analysis set	40.1
17	Same analysis set used for efficacy and safety	34.9
18	Results presented separately	68.4
19	Severity and grading of AEs	47.3
20	Provide both number of AEs and number of patients with AEs.	19.1

Issues for meta-analysis of epilepsy RCTs

Reporting

- Poor quality of reporting in places
  - Recurrent events
  - Distinguishing between patients and events
  - Definition and classification of AEs
  - Mode of collection of AEs
  - Severity of events
- Other places are not so bad
  - Title and abstract mention harms which will facilitate identification of relevant trials
  - withdrawal data and SAEs

Trial duration – median duration 28 weeks (152 trials)

- Long term effects cannot be identified

Trial size

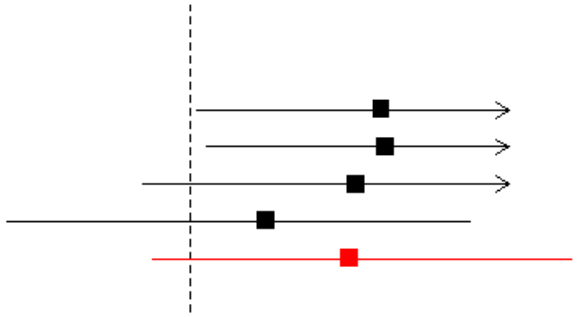
- Rare events difficult to identify
- Many trials report only the most commonly reported eg top 10% of events.

Borrowing strength from other indications

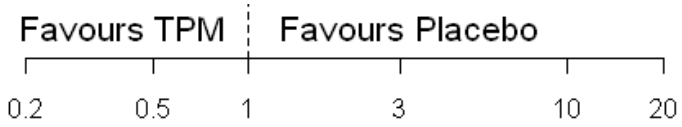
- Topiramate (TPM) licensed for use in epilepsy in 1995
- Also used to treat neuropathy and chronic headache
- We want to summarise the possible adverse events on TPM in epilepsy
- There may be limited data available for epilepsy
  - Can we look at data available from other indications?

TPM memory impairment

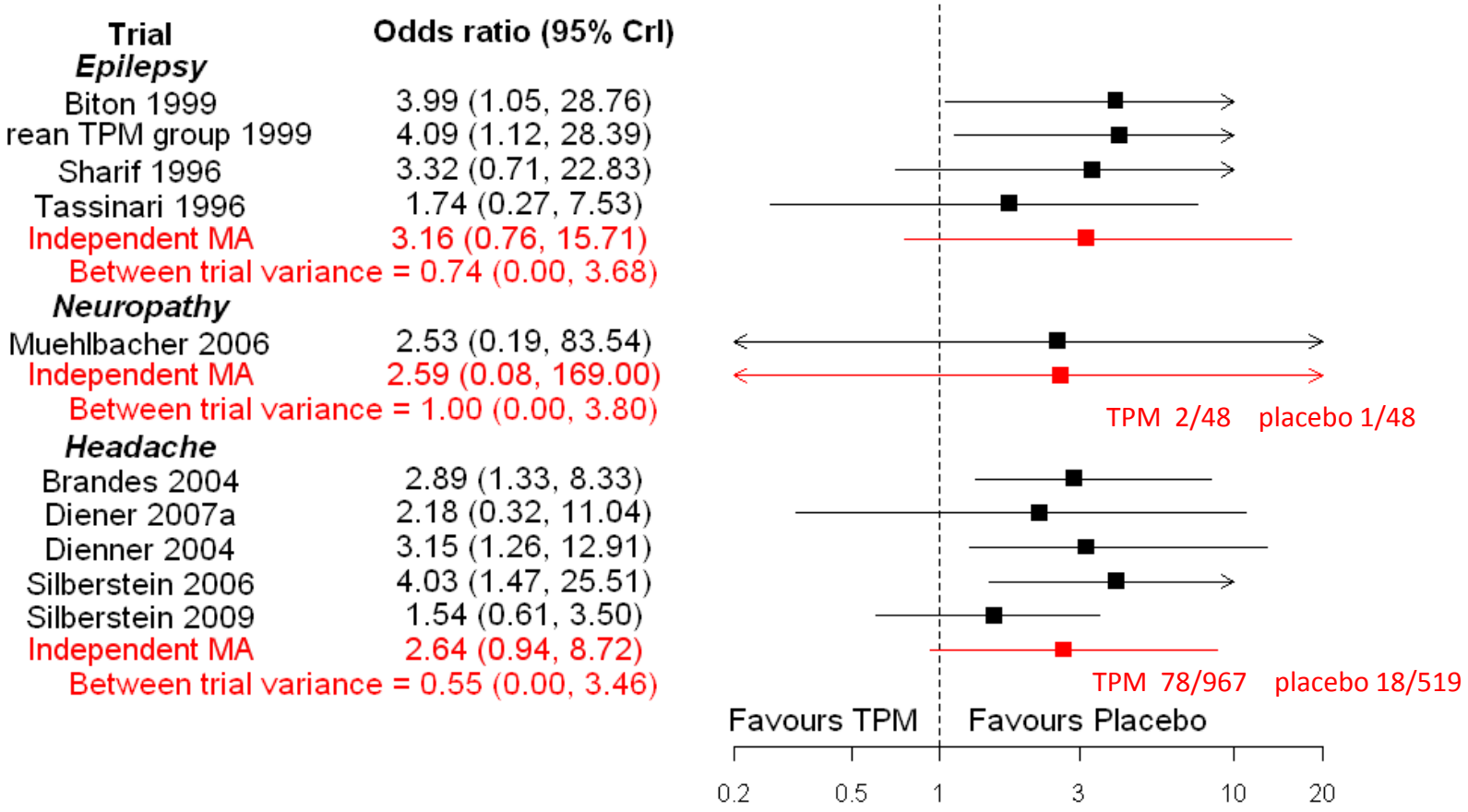
Trial	Odds ratio (95% CrI)
Epilepsy	
Biton 1999	3.99 (1.05, 28.76)
rean TPM group 1999	4.09 (1.12, 28.39)
Sharif 1996	3.32 (0.71, 22.83)
Tassinari 1996	1.74 (0.27, 7.53)
Independent MA	3.16 (0.76, 15.71)
Between trial variance = 0.74 (0.00, 3.68)	



TPM 24/183 placebo 4/181



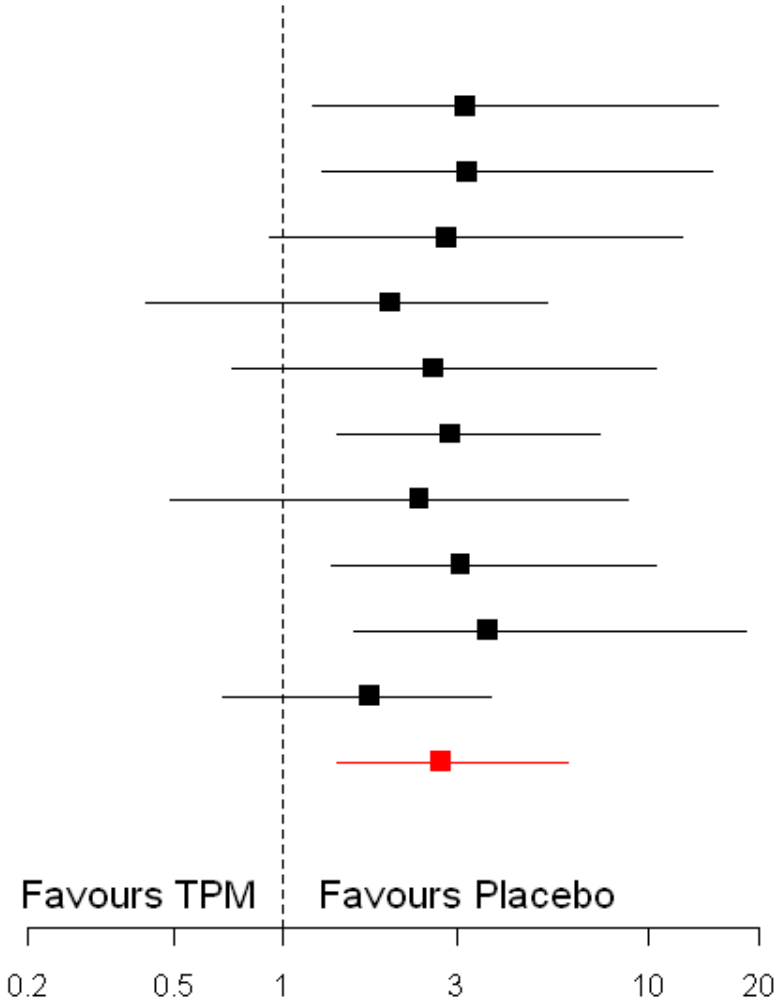
TPM memory impairment



TPM memory impairment

Trial	Odds ratio (95% CrI)
Biton 1999	3.16 (1.21, 15.47)
rean TPM group 1999	3.20 (1.27, 14.82)
Sharif 1996	2.80 (0.92, 12.27)
Tassinari 1996	1.98 (0.42, 5.27)
Muehlbacher 2006	2.59 (0.72, 10.46)
Brandes 2004	2.87 (1.40, 7.42)
Diener 2007a	2.38 (0.49, 8.76)
Dienner 2004	3.07 (1.35, 10.49)
Silberstein 2006	3.64 (1.57, 18.60)
Silberstein 2009	1.74 (0.69, 3.72)
Overall MA	2.71 (1.40, 5.97)

Between trial variance = 0.30 (0.00, 2.47)



Bayesian panoramic analysis*

$$r_{ikC} \sim Bin(n_{ikC}, \pi_{ikC})$$
$$r_{ikT} \sim Bin(n_{ikT}, \pi_{ikT})$$

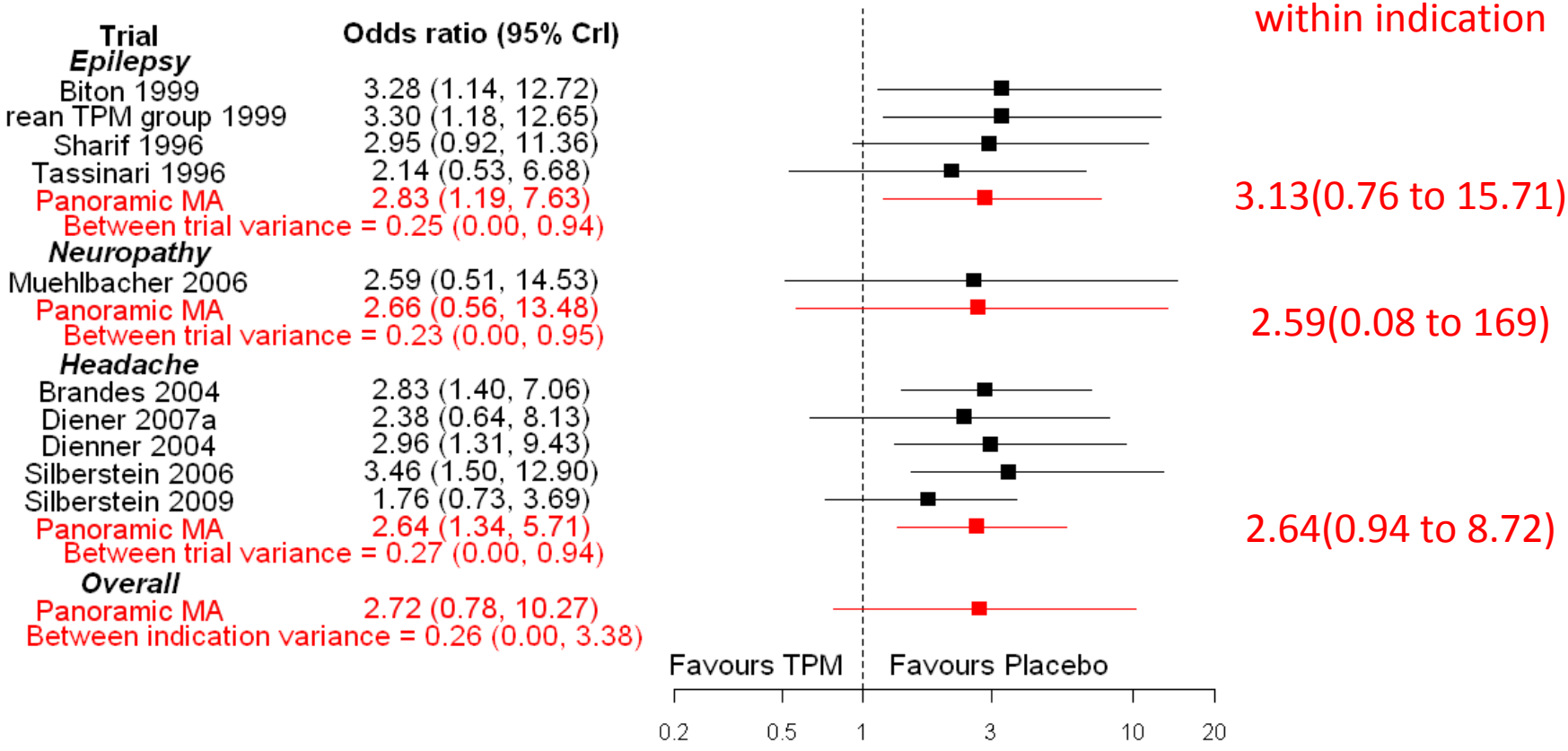
$$\begin{aligned} \text{logit } \pi_{ikC} &= \mu_{ik} \\ \text{logit } \pi_{ikT} &= \mu_{ik} + \delta_{ik} \\ \delta_{ik} &\sim N(\delta_k, \tau_k^2) \\ \delta_k &\sim N(\delta, \gamma^2) \end{aligned}$$

δ_k is the pooled effect within disease k; τ_k^2 the between study variation; and γ^2 is the between disease variation.

δ pooled estimate of treatment effect, allowing for both between and within disease variation

*Pooling systematic reviews of systematic reviews: a Bayesian panoramic meta-analysis. Hemming K, Bowaterb RJ and Lilford RL. Statistics in medicine **In press**.

Bayesian panoramic analysis



within indication

3.13(0.76 to 15.71)

2.59(0.08 to 169)

2.64(0.94 to 8.72)

Borrowing strength from other indications

Benefits

- Increase information
  - increase precision
  - may help to identify rare events
  - may help overcome problem of reporting only most common events
  - explore heterogeneity and potential effect modifiers such as dose
- Heterogeneity across indications may provide useful insight and generate hypotheses for mechanism of action?
- May help overcome limitations of the trials for the main indication?
  - poor quality
  - trial duration

Borrowing strength from other indications

Limitations

- Definition of events would need to be consistent across trials and indications
- Possibly increased heterogeneity by co-medications which may vary across indications
- More work
- Possible confounding of events with disease or event by disease interactions

Conclusions

- Synthesis of harms data for AEDs is required but is problematic
- Reporting of adverse events data is poor in places for epilepsy trials
  - Improvements are required
  - Authors and journals should be encouraged to use the CONSORT harms guideline
- Combining harms data across different indications may be beneficial
  - Particularly for newer drugs with little information

Conclusions

- Assumes treatment effects centred around a single common value across all studies and all indications– is this feasible?
- Incorporate observational data
  - Long term effects
  - Rare events
  - Teratogenic effects