# Effects of the anticonvulsant topiramate on language abilities in people with epilepsy: a cross-sectional study

Aisling Buckley, Margaret Fitzgerald, Doreen Hoerold, Gavin P Davey, Colin Doherty

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## Abstract

**Objectives: The aim of this study was to investigate the effects of topiramate (TPM) on cognitive function, specifically language, in patients with epilepsy, and to determine whether a specifically designed neuropsychological test battery can show such effects.**

**Method: Twenty patients taking TPM, 25 epilepsy controls (taking medication other than TPM) and 25 healthy controls were recruited. We used a specific neuropsychological battery, including measures of visual and verbal memory, attention, fluency and comprehension. Separate one way between group ANOVAs were performed for each neuropsychological measure.**

**Results: Bonferroni comparisons revealed that the TPM group performed significantly worse than epilepsy controls on digits forward ($p<0.001$), digits backward ($p<0.05$), controlled oral word association (COWA) ($p<0.05$) and token test ($p<0.05$). The TPM group also needed more multiple choice cues in the Boston naming test ($p<0.05$).**

**Conclusions: The present study indicates that 15% of the sample tested had impaired language abilities and raises interesting questions regarding the nature of this effect. Furthermore, we have identified some short neuropsychological tasks that can be performed in routine clinical situations that can reliably identify patients who have negative linguistic effects of TPM.**


**Key words:** Topiramate; Anticonvulsant; Neuropsychological tests; Language abilities.

## Introduction

TPM is one of a plethora of new anti-epileptic drugs (AEDs) developed in the late 1980s and early 1990s, as a result of advances in the understanding and treatment of epilepsy. A salient feature of the drug is that it can be used to treat a number of different forms of the disease, from localisation related to generalised epilepsies. The efficacy of TPM has been proven repeatedly in a number of placebo controlled, double blind trials.[1] In light of these findings, TPM is viewed as a welcome addition to the existing set of AEDs; however a number of adverse effects have been described upon administration of the drug. Central nervous system side-effects are commonly reported, including cognitive dysfunction, dizziness, headache and sedation. A recent review conducted a metanalysis of papers describing adverse effects associated with numerous new anti-epileptic drugs, citing 11 central nervous system side-effects associated with TPM.[2]

Although a range of adverse effects have been associated with the drug, including those mentioned above, language problems are a common and recurring theme amongst many papers. A 1997 review makes reference to 'hesitant speech' and 'word finding difficulties' in patients taking TPM.[3] Language regression in three children was reported as a case series in which all three patients exhibited some form of language difficulty prior to the administration of TPM.[4] In all three cases, the decline in language function proved reversible on reduction or withdrawal of TPM. This is consistently found to be the case. Based on these findings, it seems unlikely that language areas of the brain are damaged by TPM, rather language regresses due to some functional physiological interference. Several studies looking at the use of topiramate in migraine prophylaxis also found language difficulties in those taking the drug.[5,6,7] This finding effectively rules out the influence of other anti-epileptic drugs and indeed the abnormal neuronal environment in epilepsy as possible factors contributing to the effects attributed to TPM.

Our study aimed to investigate the hypothesis that in patients with cognitive side-effects of TPM, these effects could be traced back to language based dysfunction. It has been reported that a minority of subjects (ranging from 3-20%) suffer word-finding difficulties and/or fluency problems following therapy with TPM.[8,9] The study is intended to show this using a specific neuropsychological test battery, including tests of verbal and non-verbal memory, attention and language capabilities. In addition, the most sensitive tests of cognitive dysfunction will be considered as potential screening tools in the clinical setting in advance of starting patients on the drug. Importantly, the current study utilises neuropsychological tests to evaluate cognitive functions, rather than relying on subjective measures from patents.

## Methods

### Subjects

This cross-sectional study comprised 70 participants – 25 healthy controls, 25 disease controls (patients with epilepsy who were taking any medication or combination of medicines other than TPM), and 20 TPM patients. Patient characteristics are listed in *Table 1*. Exclusion criteria comprised the

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**Table 1: Presents the patient demographics - gender, age, education, Average TPM dose**

| Patient demographics | Healthy controls | Disease controls | TPM patients |
|---|---|---|---|
| N | 25 | 25 | 20 |
| Female | 19 | 13 | 13 |
| Male | 6 | 12 | 7 |
| Average age (years ± SD) | 22.04 ± 2.89 | 30.24 ± 12.036 | 32.2 ± 12.293 |
| Age range | 18-33 | 18-65 | 18-71 |
| Education (years ± SD) | 17.56 ± 1.23 | 15.08 ± 2.999 | 15.1 ± 3.878 |
| Average TPM dose (mg) | - | - | 146.87±6.03[a] |
| **Other medications:** | - | | |
| OXC N (ave. dose mg) | - | 6 (837) | 1 (1200) |
| VPA N (ave. dose mg) | - | 13 (1123) | 2 (600) |
| LTG N (ave. dose mg) | - | 7 (214) | 2 (400) |
| CBZ N (ave. dose mg) | - | 1 (2000) | 1 (1200) |
| LEV N (ave. dose mg) | | 1 (3000) | 5 (1590) |

Note: TPM, (Topiramate); SD, (Standard Deviation); OXC, (Oxcarbazepine); VPA, (Valproate); LTG, (Lamotrigine); CBZ, (carbamazepine); LEV, (Leveteracitam). [a] Average of monotherapy and polytherapy doses

presence of dementia or any learning difficulty which would interfere with the patient's ability to perform the tests, a native language other than English, or an age less than 18 years. Additionally, participants needed sufficient mobility and health to travel to the testing location. The study was passed by the ethics board of St James's hospital, Dublin 8. Each subject completed an informed consent form prior to participating in the study.

## Neuropsychological tests

All subjects underwent neuropsychological testing. The test battery included measures of non verbal memory (Rey-Osterreith complex figure test); verbal memory (California verbal learning test (CVLT)); attention (digit span, brief test of attention, trail making test) and language (controlled oral word association, Boston naming test (short version), token test).

### Data analysis

Separate one way between group ANOVAs were performed for each neuropsychological measure to investigate whether a significant difference existed between the three groups. Post hoc Bonferroni comparisons for these effects were performed to show where the differences lay and to verify that the healthy control group performed to a high standard on all tests. Unpaired t tests were used to investigate differences in the age and education levels of the two epilepsy groups. A chi square test investigated the significance of differences in the gender of the two epilepsy groups. An ANOVA was run to analyse the differences in medication of the two groups, and to investigate any possible influence of medication on the neuropsychological test results.

## Results

### Patient demographics

Gender differences between the three groups did not reach significance $X^2$ =.770, d.f =1, p>0.05. The average age and level of education of the two epilepsy groups were closely matched - independent t tests revealed that there were no significant differences for these values (age: |t|= -.538, d.f = 43, p>0.05), (education: |t|= -.020, d.f = 43, p>0.05). The healthy control category have a younger average age and higher average level of education than either of the epilepsy sets, which is consistent with their role as a confirmation of the efficacy of the test battery.

A one way analysis of variance revealed that the differing medication details of the two epilepsy groups did not reach significance, with the exception of valproate (df=39, p>0.01). In addition, a one way ANOVA comparing the age, gender, education level, medication details and score results for all tests was performed. A main effect of group was found for the following measures: digit span forwards df=39, p<0.001; digit span backwards df=39, p,0.05; FAS total df=39, p<0.5; BNT multiple choice df=39, p<0.001; Token test df=39, p<0.05. No other results reached significance.

To investigate the differences between the three groups with respect to their test scores, separate one way between group ANOVAs were performed for each neuropsychological measure. A main effect of group existed for the difference between the copy and delayed recall of the Rey–Osterrieth complex figure test (F(2,66)=5.295, p<0.05), the total number of words recalled during the CVLT (F (2,67)=5.87, p<0.05), digits forward (F(2,67)=25.11, p<0.001), digits backward (F(2,67)=8.86, p<0.001), total number of words generated in the COWA (F (2,67)=22.31, p<0.001), BNT (F(2,67)=5.39, p<0.05) and the token test (F(2,67)=6.87, p<0.05). Post hoc Bonferroni comparisons for these effects showed that in each case, the results were in favour of the healthy control group. From this point on, comparisons between the two epilepsy groups only will be made as this was the focus of the study.

### Digit span

A significant difference exists between the two epilepsy groups on measures of digits forward and digits backward. Post hoc Bonferroni comparisons show that the



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topiramate group performed worse than the epilepsy controls on both digits forward $p<0.001$, and digits backward $p<0.05$, presented in *Figures 1 and 2* respectively.

**Verbal fluency**

For the COWA, Bonferroni comparisons showed that the TPM group performed significantly worse than the epilepsy control group $p<0.05$, measured as the total number of words generated for F, A and S (*Figure 3*). For the BNT, the one way between group ANOVA found a significant difference for the overall scores (total correct). However, post hoc Bonferroni comparisons showed that the difference lies between the healthy control group and the TPM group. The BNT cues were investigated further using an unpaired t test, to investigate the difference between the two epilepsy groups on the number of cues given (*Figure 4*). A trend towards significance was seen in the values of the cues given for both semantic ($|t| = -1.745$, $d.f = 43$, $p>0.05$) and phonemic ($|t| = -1.973$, $d.f = 43$, $p>0.05$) cues. The difference between the groups for multiple choice cues did reach significance: $|t| = -2.972$, $d.f = 43$, $p<0.05$.

**Comprehension**

Bonferroni comparisons showed that the TPM group performed worse than the epilepsy controls on the Token test also ($p<0.05$). The outcome is presented in *Figure 5*, where TPM patients clearly have a lower average score on the token test, although the standard error is large.

**Number of patients affected**

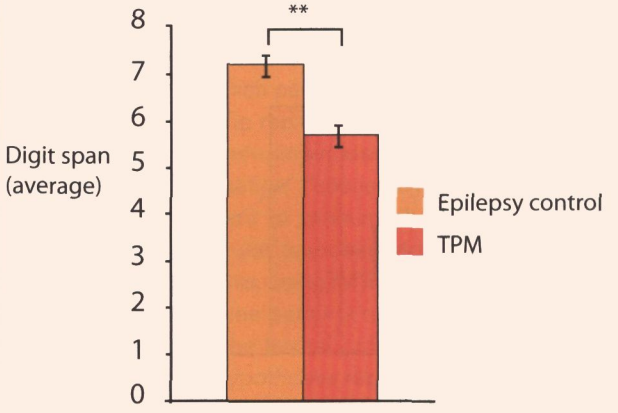
Comparisons were made for the five values for which there was a significant difference between the epilepsy and control groups – digits forward and backward, the COWA total score, the number of multiple choice cues given in the BNT and the token test. Three TPM patients each (15%, for comparison with values quoted elsewhere in the literature) were affected by the drug on the digits forward and digits backward tests (one patient in common between the two groups). Three patients (15%) were deemed to have been affected by the drug for the Total COWA score, all of whom were also >2SD below the mean for epilepsy controls for the token test. Seven patients' scores were >2SD above the epilepsy controls' mean for the number of multiple choice cues given in the BNT, 35% of the sample. Finally, six patients' comprehension abilities were affected for the token test; this constitutes 30% of the sample. These results indicate that overall approximately 15% of the sample tested had impaired language abilities and/or short-term memory and attention problems.

## Discussion

**Significant findings**

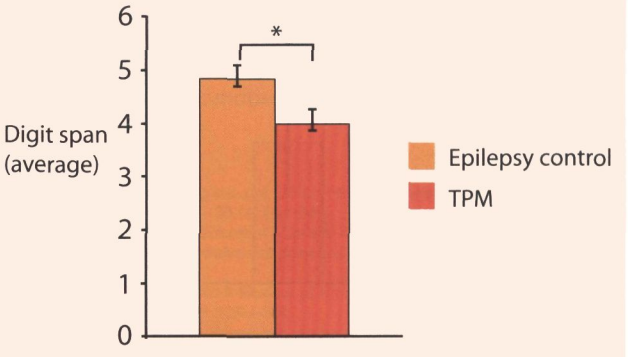
A one way analysis between groups verified that the healthy control group performed better than both epilepsy groups. The results of the tests of verbal fluency, naming ability and comprehension support the hypothesis that TPM causes language dysfunction in some epileptic patients. The results of the tests of short-term memory and attention indicate that there may be domains of cognition affected other than language, however, since these tests are essentially verbal in nature; the established language difficulties may have contributed to group differences in these areas. This is supported by the absence of significant effects in non-verbal tests of attention in these patients.

**Figure 1: Effects of the anticonvulsant TPM on Digit Span (forward)**



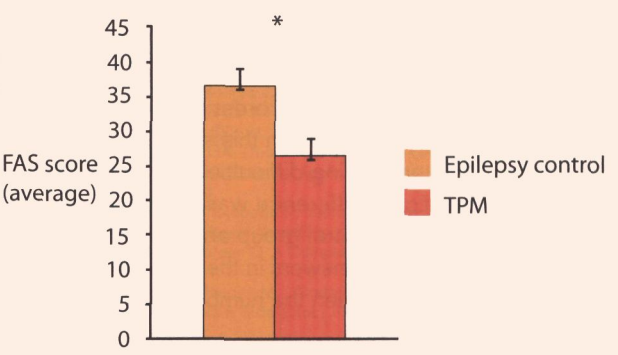

Graph represents average Digit span on the y axis vs. treatment group on the x axis. Results show a significant difference between the performances of the epilepsy control group (blue) and the topiramate group (pink). Standard error bars included. ** indicates significant difference where $p<.001$.

**Figure 2: Effects of the anticonvulsant TPM on Digit Span (backward)**




Graph shows average Digit span on y axis vs. treatment group on x axis. Results show a significant difference between the performances of the epilepsy control group (blue) and the topiramate group (pink). Standard error bars included. * indicates significant difference where $p<.05$.

**Figure 3: Effects of the AED TPM on Total No. of total words generated in COWA (FAS) test**




Graph represents total number of words generated on the y axis vs. treatment group on the x axis. The bar chart shows that the epilepsy control group (blue) performed significantly better than the topiramate treatment group (pink). Standard error bars included. * indicates significant difference where $p<.05$.



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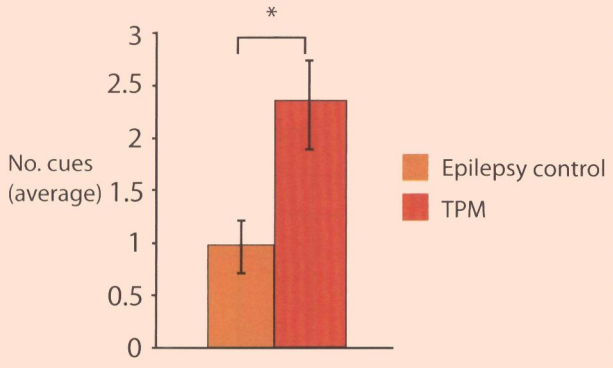
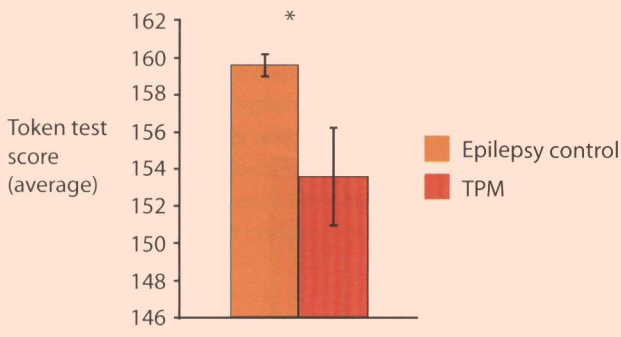
**Figure 4: Effects of the AED TPM on No. of multiple choice cues given during BNT**




Graph shows average no. of cues on y axis vs. treatment group on x axis, where epilepsy controls (blue) needed significantly less cues than the topiramate group (pink). Standard error bars included. * indicates significant difference where $p<.05$.

**Figure 5: Effects of the anticonvulsant TPM on Comprehension: Token test Scores**




Graph represents average Token Test Score on y axis vs. treatment group on x axis. Results show that the epilepsy control group (blue) performed significantly better on the test of comprehension than the topiramate set (pink). Standard error bars included. * $p<.05$.

## Verbal fluency

As predicted by the primary hypothesis, generation of words, or verbal fluency was impoverished in some patients taking TPM. This effect is evident in the results of the COWA, where a significant difference was found between the disease control patients and those receiving the drug. This finding complements previous studies in which the COWA was administered to patients taking TPM.[10] Confrontational naming is a cardinal feature of the language system and is the most sensitive test for the higher order language difficulties that are seen in clinical aphasia. In this study, our hypothesis might have predicted naming difficulties in the TPM group. However, no significant difference was found between the scores of the epilepsy control group and those taking TPM for the number of correct answers in the BNT. The results do reveal a discrepancy between the number of multiple choice cues given.

These results reflect a subtle but nonetheless greater severity of difficulty in word finding in the TPM patients. The fact that only the third cue reaches significance indicates that the epilepsy control group also had difficulty retrieving some of the words, but that they recalled the name faster than the TPM group, which eliminated the need for further prompting.

## Digit span

The divergence between the two epilepsy groups on measures of digits forward and backward suggests that there were some problems in the domain of working memory and attention, which these test are traditionally considered to measure. In light of this, it is worth noting that the functional anatomical structures implicated in problems of naming and verbal fluency in the language domain are highly likely to share resources with those parts of the frontal lobes implicated in tasks of working memory (ie. the left frontal operculum;[11] which forms part of the dorso-lateral pre-fontal cortex). As such, the effects of TPM on the language system, whether it be by a functional effect on perfusion or a biochemical effect on neurotransmission, might be expected to cause similar problems in related areas of frontal cortex. Furthermore, the finding of differences between the groups for both digit forwards and digits backwards indicates that both the phonological loop and central executive are affected by TPM usage.

## Comprehension

The token test scores are the final statistically significant results of this study. This finding indicates that the drug may have a negative impact on the patient's syntactic comprehension, ie. the ability of the participant to understand the words of a sentence in relation to each other more so than the meaning of the word. This finding is unusual, as comprehension problems are rarely quoted in the literature pertaining to TPM. One such study,[12] also utilised the token test as a measure of comprehension, this time in relation to patients taking the anticonvulsant tiagabine. The authors found a significant difference between the token test scores of the two groups, yet failed to discuss its implications fully. Again, there is a clear neuroanatomic overlap here with the poor scores in other language related tasks, in that the structures known to be involved in the functional anatomy of syntax are also located in the dominant hemisphere, left frontal opercular areas.

## Limitations

It could be argued that a particular subset of patients with one seizure type should have been included in this study, and the control group should have been composed of patients on one particular drug. However, the fact that a number of studies found different seizure types and medication to be associated with language problems suggests that language dysfunction is not associated with any one kind of seizure or concomitant medication.[13,14,9] In addition, the range of seizure types and medications included here reflects a more naturalistic clinical setting, which is useful as one aim of the study is to identify which tests best expose a problem with language to recommend for use in the clinic.

A significant difference was found between the two epilepsy groups with respect to valproate only. While it could be argued that this may have affected the results, the fact remains that one would expect any effect to occur across all types of neuropsychological measure, rather than being restricted to language measures as is the case here. In addition, it would have been impossible to match the groups



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exactly given the nature of refractory epilepsy and the diverse course of each condition. Furthermore, the analysis of variance which included medication details provided the same significant results as that which did not include them, which suggests that valproate did not have an effect on the outcome measures.

A further limitation of the study is that the tester was not blind to the medication details of the patient groups - an effect of bias cannot be ruled out as a result. Another concern is that the tests could be considered a measure of intelligence rather than specific cognitive domains. An IQ test would have corrected for this, however the level of education was noted for each patient and this can be correlated to intelligence.[15] This does not take socio-demographic effects into account, for example, during the Boston Naming Test some patients were unable to name the Sphinx; and their delay in answering may reflect the fact that they were unfamiliar with the word rather than an inability to retrieve it.

Finally, some studies which have recently been published have examined the effect of mood on neuropsychological functions, which was not considered in the present study. In one study the authors found that anxiety and depression, as measured by the Zung anxiety and Depression scales, influenced performance on the trail making test in patients taking the drug.[16] However, a study by Marino *et al*[17] found that the mood of patients correlates better with subjective measures of cognitive function that objective measure; nonetheless an assessment of mood would have been a salient addition to the project protocol.

## Clinical and research recommendations

One aim of this study was to evaluate the ability of the tests included in the battery to identify problems with language. The results of the study show that the COWA, token test, and digits forward/backward are the most useful in showing these effects. Each of these tests is quick to administer, as this was a requirement of their inclusion. The token test requires elaborate materials and therefore is probably not convenient for use in a clinical setting. The COWA and digits forward/backward are easily administered and scored, to give a quick indication of whether the drug is causing an affect. A score of 15 or less for the total of the three COWA values (F-A-S) could be considered problematic as this is 2SD below epilepsy controls. A score of 4 or less for digits forward and 2 or less for digits backward could likewise be considered an indication of abnormal abilities.

The finding that approximately 15% of patients fall more than 2SD below the epilepsy control averages for the COWA verifies that the drug affects the language abilities of at least some patients. This figure agrees well with others quoted in the literature.[8,9,16] This raises the question of why these patients in particular are affected. It may be a pharmacogenomic interaction between the drug and the genetic background of this minority, or an interaction between TPM and a particular area of the brain (namely the left frontal cortex), causing a functional, biochemical or perfusion difference. This question could be investigated further by developing a series of language tests suitable for use within an fMRI scanner, and to administer them to patients.

This study identifies and confirms that TPM is in general a safe and efficacious addition to already existing AEDs. However, a small minority of patients (c. 15%) will suffer from some form of cognitive difficulty – largely language related. Memory and concentration do not appear to be affected. Simple tests of verbal fluency and working memory, which can easily be administered in a clinical setting, should prove sufficient to identify which patients have this difficulty.

In addition, a specific region of the brain, namely the left frontal cortex, has been implicated as a target of TPM's effect on language function. Functional magnetic resonance imaging can be utilised to examine the neuroanatomical, biochemical and vascular responses to the drug. A recent study has addressed this, using fMRI to investigate language disturbances in migraine patients taking TPM.[18] While only the results involving the frontal cortex have been reported thus far, they permit hypotheses regarding TPM's effects to be drawn. The authors find that in patients taking TPM, who have complained of language difficulties, Brodmann's area 44 is seen to be under active, while other areas are over active – possibly as a result of compensation. They suggest that this may represent a reorganisation of the language network in these patients. Again, further studies will be needed to verify this claim and to contextualise it in light of what is known about TPM's cognitive effects to date.

Declaration of Interest: Colin Doherty has been on advisory boards for UCB pharma, Novartis, Esai and GlaxoSimithKline. He has received unrestricted educational grants from Janssen-Cilag and Lundbeck.

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Under the Abstract heading of Method, include wherever applicable the study design, setting, patients/participants (selection criteria, description), interventions, observational and analytical methods and main outcome measures. For review articles specify the methods of literature search and selection. Under the Abstract heading of Results, give the most important specific data together with their statistical significance.

Figures and graphs should be clear and of good quality, and should be accompanied by relevant data to facilitate redrawing where necessary. All materials sent for publication should be accompanied by a covering letter signed by all the authors, and such material will become the property of the Journal until, and if, publication is refused. Material so referred should not be sent elsewhere for publication. Hard copies and the original covering letter should be emailed to: **psychological@medmedia.ie** Full postal address, telephone numbers etc. should be included.

## References

Timely references should highlight the study's relevance to current research or clinical practice. References to journal articles[1-3] and to books[4-6] illustrate the 'Vancouver' style,[1] ie. number references in the order they appear in the text, do not alphabetise. Journal titles should be abbreviated as in *Index Medicus*. The Uniform requirements for manuscripts submitted to biomedical journals[5] has two paragraphs on statistical guidelines. These have been explained by Bailar and Mosteller.[3]

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In the interests of accountability and credibility all financial/material support for the work should be clearly stated.[7] Authors of original data must take responsibility for the integrity of the data and accuracy of the data analysis. All authors must have full access to all the data in the study.[8] Conflict of interest exists when an author (or the author's institution), reviewer, or editor has financial or personal relationships that inappropriately influence (bias) his or her actions (such relationships are also known as dual commitments, competing interests, or competing loyalties).[9]

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## Acknowledgments

Authors should obtain permission from those named in Acknowledgments, since readers may infer endorsement.


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