PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of clinical trial findings on Bell's palsy management in General Practice in the United Kingdom 2001-2012: interrupted time series regression analysis.
AUTHORS	Morales, Daniel; Donnan, Peter; Daly, Fergus; van Staa, Tjeerd; Sullivan, Frank

VERSION 1 - REVIEW

REVIEWER	Orlando Guntinas-Lichius Professor and Chairman ENT Department University Hospital Jena Germany No conflict of interests.
REVIEW RETURNED	06-May-2013

GENERAL COMMENTS	There is not much knowledge on the incidence of Bell's palsy. There was up to now no knowledge if the ground-breaking Scottish and Swedish studies have influenced the treatment in daily routine. Therefore the presented study is very valuable. Introduction: "… Bell's palsy (acute idiopathic facial paralysis) …" – Definition is wrong; paralysis = complete palsy; an acute idiopathic facial paresis, i.e. an incomplete palsy would also be a Bell's palsy. Introduction: "Large population based studies of Bell's palsy (acute idiopathic facial paralysis) are rare and published incidence rates inconsistent, varying from as low as 11 per 100,000 to 51.9 per 100,000 person-years.[12-18]" Be more critical: not all cited studies are large population bases studies with good methodology. Methods: "The study population consisted of all patients ≥16 years of age" why did the authors choose this cut-off? Please explain, there are also some Bell's palsy cases in younger patients. Methods: "with at least one year of up to standard medical history" to be sure: please clarify: do you mean 1 year history backwards, or 1 year follow-up? Methods: "New Bell's palsy cases were defined by an incident Read code for Bell's palsy in patients" – for readers outside the UK need more information: Is this the initial diagnosis? or a final diagnosis after complete work-up? Discussion: I miss a discussion of the accurateness of the diagnosis "Bell's palsy" by a GP. Bell's palsy is a diagnosis of exclusion. What do you about the diagnostic extent? Is the EMR giving data on the diagnostic tools used? Discussion: "Older patients, the main differential diagnosis of Bell's palsy is stroke which may have resulted in more patients receiving treatment from secondary care services." – This this really the only reason for a possible underestimation? Who is treating patients with

	Bell's palsy in the UK? Just telling "Given the low rate of referrals to ENT, ophthalmology and neurology specialities" is not enough. Please give clear numbers for the rate of referrals to other disciplines and cite literature, please. Discussion: "Although most Bell's palsy cases will resolve spontaneously, full recovery is more likely and quicker in those treated with prednisolone. This is important as around 30% of untreated patients will suffer long term problems including facial disfigurement potentially complicated by facial contracture, reduced sense of taste, speech problems, eye-mouth synkinesias, corneal ulceration and adverse psychological impact." – This is a contradiction: How can MOST case resolve spontaneously but 30% will suffer from defective healing! Discussion, untreated cases: The number of untreated cases is surprisingly high. The cited evidence based literature is based on a treatment with 72 hours. What do you know about the time interval between onset and diagnosis of the GP? There might be many patients which are diagnosed later than 72 hours.

REVIEWER	Dr David Allen Consultant Clinical Neurophysiologist Wessex Neurological Centre University Hospitals Southampton UK I have no conflicts of interest.
REVIEW RETURNED	21-May-2013

RESULTS & CONCLUSIONS	Although the statistics demonstrate significane, when one considers the data as presented in figure 2, it is difficult to see a clear change in prescribing behaviour in 2010, that was not already occurring, that is a fluctuating but gradually increasing use of prednisolone, after a decreasing use from 2001 to 2005. In addition in the discussion the authors comment that the use of steroids increased by 88%, in the paragraph which begins 'the SBPS was associated with a signifiacnt clinical impact...' implying in my view that this was related. Only a stepwise change at the time of publication and any subsequent trend can be attributed to the trial itself. This appears a little misleading.
GENERAL COMMENTS	Dr Morales and colleagues present an interesting paper on a subject that should attract more attention. Clinical trials demonstrating significant results such as the SBPS should be associated with changes in practice, yet this does not necessarily appear to be the case. Further study to explore the reasons for this should be encouraged. They fulfil their first objective very well by producing a likely accurate incidence figure for Bell's palsy in the UK. Their second objective is more challenging. They concede that the study can only offer association and not evidence of cause and effect. It might be of interest to delve a little deeper here, though I appreciate that historical interview is fraught with amnesia and bias, to attempt to assess why the prescribing choice was made on an individual basis.

	The authors commence the introduction by comparison with a cardiovascular trial. I would like to see this explored more if possible. Though the incidence of cardiovascular and oncology diseases are higher and no doubt the associated drug funding/promotion also higher, it would be of interest to compare the effects of some of the major trials in these areas, with respect to impact upon prescribing. The results suggest a stepwise change of 5% in prescribing immediately following the trial. That and subsequent trend, must be the best measure of effect. Later, in the discussion, it is not clear and it appears that an effect from 2005 to 2010 is attributed to the the trial.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Orlando Guntinas-Lichius
Professor and Chairman
ENT Department
University Hospital Jena
Germany

No conflict of interests.

1. "There is not much knowledge on the incidence of Bell's palsy. There was up to now no knowledge if the ground-breaking Scottish and Swedish studies have influenced the treatment in daily routine. Therefore the presented study is very valuable. Introduction: "… Bell's palsy (acute idiopathic facial paralysis) …" – Definition is wrong; paralysis = complete palsy; an acute idiopathic facial paresis, i.e. an incomplete palsy would also be a Bell's palsy."

We have changed the wording to '(acute idiopathic facial palsy)' Page4,Line16

2. "Introduction: "Large population based studies of Bell's palsy (acute idiopathic facial paralysis) are rare and published incidence rates inconsistent, varying from as low as 11 per 100,000 to 51.9 per 100,000 person-years.[12-18]" Be more critical: not all cited studies are large population bases studies with good methodology."

We have included the following sentence:
'In addition, not all published studies are large population based studies and variations in sampling technique may bias measures of disease occurrence.' Page1,Line19-21.

3. "Methods: "The study population consisted of all patients ≥16 years of age" why did the authors choose this cut-off? Please explain, there are also some Bell's palsy cases in younger patients."

We acknowledge that Bell's palsy may occur in younger patients. However, we were interested in measuring the incidence in adult patients in which Bell's palsy is much more likely to occur. As we demonstrate, the recorded incidence of Bell's palsy is strongly associated with age and cases in younger patients are likely to be much rarer. Also, NICE Clinical Knowledge Summaries provide advice about Bell's palsy treatment in patients aged 16 years onwards (http://cks.nice.org.uk/bells-palsy#!scenario).
Unfortunately our data only includes patients >=16 and we are unable to provide further incidence rates for patients <16years which is a limitation of the study. We have made this more explicit in the article focus & in the discussion by including the following.
'Bell's palsy may occur rarely in children however the vast majority of cases will occur in adults and

increases substantially with age. Acute idiopathic facial palsy in children is more likely to be managed in secondary care, from which no prescribing data is available. As such, inclusion of patients assessing the impact of clinical trial data would likely underestimate the true impact of clinical trial findings.' Page14,Line10-14.

4. "Methods: “with at least one year of up to standard medical history” to be sure: please clarify: do you mean 1 year history backwards, or 1 year follow-up?"

We mean 1 year history backwards and we have clarified this in the manuscript.Page6,Line14.

5. "Methods: “New Bell’s palsy cases were defined by an incident Read code for Bell’s palsy in patients” – for readers outside the UK need more information: Is this the initial diagnosis? or a final diagnosis after complete work-up?"

It is not possible to answer this question using the existing data. For this reason we included prescriptions issued within a seven day period before and after the date of Bell’s palsy recording. We have made this explicit in the discussion.
'We are unable to ascertain whether or not the diagnosis of Bell’s palsy was recorded at initial presentation or following complete investigation. For this reason, we included prescriptions issued within a seven day period before and after the date of Bell’s palsy recording.' Page15,Line1-4.

6. "Discussion: I miss a discussion of the accurateness of the diagnosis “Bell’s palsy” by a GP. Bell’s palsy is a diagnosis of exclusion. What do you about the diagnostic extent? Is the EMR giving data on the diagnostic tools used?"

We state in the discussion that Bell’s palsy cases were diagnosed by family physicians in real life settings and no scale was used to quantify the degree of facial nerve dysfunction. We have no information pertaining to the extent of investigation patients may have undergone or their results. Current clinical evidence demonstrates the benefit of early treatment for Bell’s palsy (<=72 hrs). Theoretically it is possible that referring patients for a full work up could be one reason for untreated cases.

7. "Discussion: “Older patients, the main differential diagnosis of Bell’s palsy is stroke which may have resulted in more patients receiving treatment from secondary care services.” – This this really the only reason for a possible underestimation?"

We also highlight in the limitations that treatment could have occurred from other sources (e.g. accident and emergency units) which could result in a possible underestimation.

8. "Who is treating patients with Bell’s palsy in the UK? Just telling “Given the low rate of referrals to ENT, ophthalmology and neurology specialities” is not enough. Please give clear numbers for the rate of referrals to other disciplines and cite literature, please."

We do not have any data for referrals to other disciplines and have included the following statement to acknowledge this in the discussion. We have also included ‘in General Practice’ in the manuscript title.
'Although it would appear from the low rate of referrals to ophthalmology, ENT and neurology that Bell’s palsy is primarily managed in primary care, we cannot exclude the possibility that patients were referred to other disciplines potentially underestimating the number of referrals.' Page15,Line8-11.

9. "Discussion: “Although most Bell’s palsy cases will resolve spontaneously, full recovery is more likely and quicker in those treated with prednisolone. This is important as around 30% of untreated

patients will suffer long term problems including facial disfigurement potentially complicated by facial contracture, reduced sense of taste, speech problems, eye-mouth synkinesias, corneal ulceration and adverse psychological impact.” – This is a contradiction: How can MOST case resolve spontaneously but 30% will suffer from defective healing!"

We use the term ‘most’ to represent >50%. We have changed this term to ‘majority’ to be more explicit.Page15,Line17.

10. "Discussion, untreated cases: The number of untreated cases is surprisingly high. The cited evidence based literature is based on a treatment with 72 hours. What do you know about the time interval between onset and diagnosis of the GP? There might be many patients which are diagnosed later than 72 hours."

We agree with the reviewers comment. For this reason we pre-specified the time interval to include treatment prescriptions issued within seven days before and after the date of Bell’s palsy recording (a 14 day window in total) as mentioned in an earlier response.

Reviewer: Dr David Allen
Consultant Clinical Neurophysiologist
Wessex Neurological Centre
University Hospitals Southampton
UK

I have no conflicts of interest.

1. "Although the statistics demonstrate significane, when one considers the data as presented in figure 2, it is difficult to see a clear change in prescribing behaviour in 2010, that was not already occurring, that is a fluctuating but gradually increasing use of prednisolone, after a decreasing use from 2001 to 2005."

Our interpretation of figure 2 is that following the Cochrane reviews, prednisolone only therapy appears to gradually fall then plateau until the 2007 SBPS is published. The trend in prednisolone only therapy then increases. We have included the following statement in the discussion:
‘In addition, there is a suggestion that the rising trend in prednisolone only therapy and falling trend in combination therapy over the last year of observation is plateauing, which may be an effect related to the time since publication.’Page12,Line4-7.

2. "In addition in the discussion the authors comment that the use of steroids increased by 88%, in the paragraph which begins 'the SBPS was associated with a signifiacnt clinical impact...' implying in my view that this was related. Only a stepwise change at the time of publication and any subsequent trend can be attributed to the trial itself. This appears a little misleading."

We agree with the reviewers comment. We have amended the relevant paragraph as follows:
‘The SBPS was associated with a significant clinical impact on Bell’s palsy management by increasing treatment with corticosteroids and reducing combination therapy with antivirals based upon the results of time series regression analysis. Use of prednisolone alone increased by 70% from the point immediately before publication of the SBPS to the highest point in 2010. Conversely, combination therapy fell by 41% from the point immediately before publication of the SBPS to the lowest point in 2010.’ Page10,line7-13.

3. "Dr Morales and colleagues present an interesting paper on a subject that should attract more

attention. Clinical trials demonstrating significant results such as the SBPS should be associated with changes in practice, yet this does not necessarily appear to be the case. Further study to explore the reasons for this should be encouraged.They fulfil their first objective very well by producing a likely accurate incidence figure for Bell's palsy in the UK.Their second objective is more challenging. They concede that the study can only offer association and not evidence of cause and effect. It might be of interest to delve a little deeper here, though I appreciate that historical interview is fraught with amnesia and bias, to attempt to assess why the prescribing choice was made on an individual basis."

The reviewer raises an interesting point but unfortunately we cannot answer this point with the data currently available. Further research into this area is currently being planned in an attempt to address some of these issues.

4. "The authors commence the introduction by comparison with a cardiovascular trial. I would like to see this explored more if possible. Though the incidence of cardiovascular and oncology diseases are higher and no doubt the associated drug funding/promotion also higher, it would be of interest to compare the effects of some of the major trials in these areas, with respect to impact upon prescribing."

We have included the following statement in the discussion:
'Relatively few studies have attempted to evaluate the impact of clinical trials on clinical practice. The ALLHAT trial was a large randomised double-blind trial in which the study doxazosin arm was terminated early due to an unfavourable risk of cardiovascular events compared to treatment with chlorthalidone. The ALLHAT trial was associated with a 26% reduction in annual alpha-blocker prescription orders, a 22% reduction in dispensed alpha-blocker prescriptions and a 54% reduction in physician reported alpha-blocker drug-use in the US.[4] Despite the clinically significant reductions, significant numbers of hypertensive patients still received treatment with alpha-blockade and it was proposed that further strategies are required to increase the impact clinical trial findings should have. Our study observed similar findings in that although a clinically significant impact occurred, clinical evidence was not fully adopted.' Page12,Line9-19.

5. "The results suggest a stepwise change of 5% in prescribing immediately following the trial. That and subsequent trend, must be the best measure of effect. Later, in the discussion, it is not clear and it appears that an effect from 2005 to 2010 is attributed to the the trial."

We agree with the reviewers comment and refer the editor back to the response to reviewer 2's second comment were we clarify this in the discussion in relation to publication of the SBPS.

VERSION 2 – REVIEW

REVIEWER	Orlando Guntinas-Lichius University Hospital Jena, ENT Department No conflict of interests
REVIEW RETURNED	08-Jun-2013

- The reviewer completed the checklist but made no further comments.