

Institution: University of Dundee
Unit of Assessment: UoA2 Public Health, Health Services and Primary Care
Title of case study: Changing clinical practice in Bell's Palsy: the impact of a clinical trial highlighting the impact of evidence for primary care
1. Summary of the impact

This multicentre research study, led by **Sullivan** (University of Dundee), demonstrated that in patients with Bell's Palsy (where no best treatment had been defined), early treatment with prednisolone significantly improved the chances of complete recovery at three and nine months. Furthermore, this complex randomised controlled trial, recruiting 551 incident cases from primary care, demonstrated no evidence of benefit from aciclovir alone, or in combination with prednisolone. The findings led to revisions in the Cochrane reviews on the subject and have been incorporated into national and international guidelines. Substantial changes in prescribing practice for Bell's Palsy and reduced hospital referrals in the UK have been demonstrated as a direct result of publication of this study.

2. Underpinning research

The annual incidence of Bell's Palsy is approximately 38/100,000; one person in sixty will develop this condition during their lifetime. Although many cases resolve spontaneously around 25% have a poor outcome with persistent facial nerve malfunction and deformity. Its aetiology is unknown but the dominant hypothesis before our study was that viral reactivation caused oedematous swelling of the facial nerve within the temporal bone. This was assumed to cause distal denervation of motor (and sometimes sensory) fibres. Prior to publication of our Scottish Bell's Palsy Study paper in the *New England Journal of Medicine* [i] in 2007, two Cochrane reviews, published in 2002 and updated in 2004 [ii, iii], found an insufficiency of high quality evidence and concluded that more data were needed to determine whether early treatment with steroids and/or antivirals for Bell's Palsy was effective in reducing poor outcomes. In the face of this uncertainty increasing amounts of expensive antiviral drugs were being prescribed.

We undertook pilot work in the emergent Primary Care Research Networks of Tayside and the West of Scotland to scope the feasibility of a study to examine the effect of different treatments on outcomes in Bell's Palsy.

The Scottish Bell's Palsy study was led by the University of Dundee; the lead researcher was **Sullivan** and other key researchers in Dundee were **Smith** (local Principal Investigator in Grampian), **Donnan** (Study Statistician), **Clarkson** (UoA3, co-ordinated dental participation) and **Daly** (Trial Manager). It was a collaboration built around the Scottish School of Primary Care, with other University partners including Swan and Morrison (Glasgow), McKinstry and Davenport (Edinburgh) and Vale (Aberdeen).

The key features of the underpinning science developed through this work were that:

- a) There was genuine uncertainty about how to manage this acute, distressing condition;
- b) It was a national, acute, primary care trial involving GPs in half of all practices in Scotland;
- c) It had a primary outcome measure that was highly relevant to patients, clinicians and policymakers: complete recovery at three and nine months;
- d) It recorded and reported adverse events;
- e) It used an intention-to-treat analysis;
- f) The results were presented in a variety of ways to aid understanding. In addition to odds ratios, we also provided Absolute Risk Reduction and Numbers Needed to Treat and an economic analysis;

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- g) The conclusion was clear: early treatment with prednisolone significantly increased chances of complete recovery at three and nine months. In contrast, aciclovir had little or no effect [iv];
- h) Implementing the result is cost-effective and does not require the health service to be reorganised; a GP simply prescribes a single, relatively inexpensive drug instead of a relatively expensive drug or a combination [v].

We therefore rejected the hypothesis that the aetiology of Bell's Palsy is reactivation of the Herpes Simplex Virus affecting the facial nerve. The specific contribution of this study is that prednisolone (50mg/day for 10 days) significantly improves outcomes (83.0% recovery to a House Brackmann Grade of I at 3 months for prednisolone compared with 63.6% for no prednisolone) and antivirals confer no additional advantage. The Numbers Needed to Treat for treatment with oral corticosteroids were six (95% Confidence Interval 4 to 9) at three months and eight (95% CI 6 to 14) at nine months.

3. References to the research

- i. **Sullivan FM**, Swan IRC, **Donnan PT**, Morrison JMM, **Smith BH**, McKinstry B, Davenport RJ, Vale LD, Clarkson JE, Hammersley V, Hayavi S, **Daly FD** (2007) Early treatment with prednisolone or acyclovir in Bell's palsy. *N. Engl. J. Med.* **357**, 1598-607 (DOI: 10.1056/NEJMoa072006).
- ii. Salinas RA, Alvarez G, **Daly F**, Ferreira J (2004) Corticosteroids for Bell's palsy (idiopathic facial paralysis). *Cochrane Database of Systematic Reviews* 2004 Issue 2:CD001942. (DOI: 10.1002/14651858.CD001942.pub2).
- iii. Allen D, Dunn L (2004) Aciclovir or valaciclovir for Bell's palsy (idiopathic facial paralysis). *Cochrane Database of Systematic Reviews* 2004 Issue 1:CD001869. (DOI: 10.1002/14651858.CD001869.pub2).
- iv. **Sullivan F**, Swan I, **Donnan P**, Morrison J, **Smith B**, McKinstry B, Davenport R, Vale L, Clarkson J, Hernández R, Stewart K, Hammersley V, Hayavi S, McAteer A, Gray D, **Daly F** (2009) A randomised controlled trial of the use of aciclovir and/or prednisolone for the early treatment of Bell's palsy: the BELLS study. *Health Technol. Assess.* **13** No.47 (DOI: 10.3310/hta13470).
- v. Hernández R, **Sullivan F**, **Donnan P**, Swan I, Vale L for the BELLS Trial Group (2009) Economic evaluation of early administration of prednisolone and/or aciclovir for the treatment of Bell's palsy. *Fam. Pract.* **26**,137-44 (DOI: 10.1093/fampra/cmn107).

Funding

- **Sullivan, F.**, Morrison, J., Swan, I., Cairns, J., Donnan, P., Smith, B., McKinstry, B. and Davenport, R: A national multicentre, factorial trial of the early administration of steroids and/or antivirals for Bell's Palsy Health Technology Assessment Board; (2003-2007) £658,347.

4. Details of the impact

The direct clinical impact this trial had on Bell's Palsy management in UK General Practice was measured by analysing trends in prescribing behaviour (with significance confirmed by interrupted times series regression analysis) between 2001 and 2012 [1]. This analysis used 14,460 Bell's Palsy cases identified from the Clinical Practice Research Datalink database (5.25 million active UK electronic medical records), and clearly demonstrated that the trial was associated with a significant increase in treatment with prednisolone and reduction in combination treatment with antivirals, the maximum relative increases and decreases being 70% and 41% respectively. These significant changes in clinical behaviour began very soon after publication of the clinical trial in October 2007 and were in line with trial recommendations. The use of more effective early therapy was associated with a reduction in referrals to hospital by 36% (from 9.2% to 5.9% of incident cases).

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The wider impact of the study is on management of Bell's Palsy with clinical guideline recommendations to avoid unnecessary medication, and the establishment of a strong clinical research network able to undertake methodologically rigorous work in Primary Care in Scotland.

As soon as the results of the main study were published in the *New England Journal of Medicine* there was considerable press interest internationally involving print, radio and television (BBC). This paper has been cited by many other groups studying Bell's Palsy and related conditions with commentaries in major journals such as the *Lancet*. To date (16.10.13), the paper has been cited 270 times.

As a result of the findings, the Cochrane Collaboration recognized the need to update the previous reviews of antivirals and steroids in Bell's Palsy. Our group was given responsibility for keeping the former up to date [2] and collaborates with colleagues in Chile on the latter [3]. This is being updated again in 2013 and an individual patient meta-analysis is being prepared studying the experience of the most severely affected patients. This will involve a reanalysis of patients in this study and severely affected cases in Scandinavia and South Korea, and may lead to further trials of candidate interventions for severe disease. We have also been commissioned by the Cochrane Neuromuscular Review Group at King's College London to prepare an overview of all interventions in Bell's Palsy. The Royal College of General Practitioners, Academy of Medical Royal Colleges and Sense About Science used this study in *Evidence Based Medicine Matters* as one of 15 case studies of the "game changers in evidence based medicine", highlighting it as an example of an evidence-based approach to general practice [4].

We disseminated the results of our study to patients and clinicians in Scotland who had been directly involved and sent briefing notes to policy makers in the UK. We also presented the findings at a number of primary care and specialist conferences and were invited to present the results in prestigious lectures in the UK and overseas. Professional recognition of the quality and impact of the research included awards from the RCGP (UK) Medical Association (<http://thebmjawards.bmj.com/previous-winners/2009/research-paper-of-the-year>) for the best research published in the year of award [4].

The findings have been incorporated into NHS and international guidelines (e.g. in India, Spain, Ireland) [5-8] providing advice to clinicians and patients in a range of formats (BMJ Point of Care series, BMJ Best Practice Series, BMJ Clinical Evidence, RCP Map of Medicine Project) and the study has been selected by the National Institute for Health Research as an exemplar project.

This clinical trial has contributed to the reputation of the NHS-funded Scottish Primary Care Research Network and Tayside Academic Health Science Collaboration. These facilitate collaboration between front-line clinicians and academics, which is often difficult; in fact half of all clinical trials fail to recruit adequate numbers of study subjects [9].

In summary, we led a complex and collaborative randomised controlled trial that enrolled acute cases of Bell's Palsy through a nationwide research network, providing and disseminating clear results, both to clinicians and the general public [10]. This project had a beneficial impact on the evidence base for primary care internationally. It has led directly to cost effective changes in prescribing practice which produce clear patient benefit.

5. Sources to corroborate the impact

1. Morales D, **Donnan PT**, **Daly F**, Staa TV, **Sullivan FM** (2013) Impact of clinical trial findings on Bell's palsy management in general practice in the UK 2001-2012: interrupted time series regression analysis. *BMJ Open* **16**, 3:e003121 (DOI:10.1136/bmjopen-2013-003121).
2. Lockhart P, **Daly F**, Pitkethly M, Comerford N, **Sullivan F** (2009) Antiviral treatment for Bell's palsy (idiopathic facial paralysis). *Cochrane Database of Systematic Reviews* 2009 Issue 4: CD001869 (DOI: 10.1002/14651858.CD001869.pub4).
3. Salinas RA, Alvarez G, **Daly F**, Ferreira J (2010) Corticosteroids for Bell's palsy (idiopathic facial paralysis). *Cochrane Database of Systematic Reviews* 2010 Issue 3:CD001942. (DOI: 10.1002/14651858.CD001942.pub4).

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4. Sense About Science, Academy of Medical Royal Colleges. Evidence Based Medicine Matters. London: Sense About Science, April 2013.
<http://www.aomrc.org.uk/about-us/news/item/evidence-based-medicine.html>;
<http://www.senseaboutscience.org/data/files/resources/124/Evidence-Based-Medicine-Matters.pdf>.
5. <http://www.patient.co.uk/doctor/facial-nerve-palsy>;
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3152161/>;
<http://emedicine.medscape.com/article/1146903-treatment>;
http://www.eguidelines.co.uk/eguidelinesmain/gip/vol_10/may_07/jaunoo_bells_may07.php#.UkmXvYYqiSo.
6. National Institute for Health and Care Excellence (NICE):
<http://cks.nice.org.uk/bells-palsy#!scenariobasis:1>
<http://cks.nice.org.uk/bells-palsy#!references>;
 NHS Choices (for patients):
<http://www.nhs.uk/Conditions/Bells-palsy/Pages/Treatment.aspx>.
7. GPNotebook: <http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20101006114225162451>.
8. 5Minute Clinical Consult: http://www.unboundmedicine.com/5minute/ub/view/5-Minute-Clinical-Consult/116074/6/bell_palsy.
9. Treweek S, Mitchell E, Pitkethly M, Cook J, Kjeldstrøm M, Taskila T, Johansen M, **Sullivan** F, Wilson S, Jackson C, Jones R (2010) Strategies to improve recruitment to randomised controlled trials. *Cochrane Database of Systematic Reviews* 2010 Issue 1:MR000013. (DOI: 10.1002/14651858.MR000013.pub4) (Colloquium presentation).
10. Further examples of lay press reporting impact of the study:
<http://www.facialpalsy.org.uk/about-us/media-centre/press-releases/150813-facing-facts-44-of-bells-palsy-patients-do-/440>;
<http://medicalxpress.com/news/2013-07-bell-palsy-treatment.html>