Institution: Newcastle University

Unit of Assessment: UoA 4

Title of case study: Approval of the first licensed medication to treat drooling in children with neurodisability

Period when the underpinning research was undertaken: 2012-2018

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor Jeremy Parr	Professor of Paediatric Neurodisability	January 2009-present
Professor Allan Colver	Emeritus Professor of Community Child Health	1997-2012 honorary contract; 2012-2017 full contract.
Dr Lindsay Pennington	Reader in Communication Disorders	September 2001-present
Dr Emma Todhunter (Weldon)	Clinical Research Associate	September 2013-December 2018
Dr Nick Steen	Senior Statistician	November 1994-July 2018
Dr Deborah Stocken	Senior Lecturer, then Professor and Visiting Researcher	June 2012-July 2017, July 2017-June 2020
Mr Mike Cole	Statistician	June 1989-present

Period when the claimed impact occurred: January 2017-present.

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Neurodevelopmental conditions account for the majority of disability in children, and a common symptom is severe and chronic drooling. Drooling is associated with social embarrassment, increased carer burden and a risk of pneumonia. Newcastle research identified that one type of medication used to treat drooling (glycopyrronium bromide, GBr) had fewer side effects, such as dry mouth, pupil dilation and seizures, compared to the most frequently prescribed treatment in the UK (hyoscine). This finding informed the 2017 NICE recommendation that GBr be brought in line with hyoscine as a single first-line treatment. In addition, Newcastle research underpinned the MHRA approval of two proprietary GBr drugs; of which one further received EMA, Scottish and Dutch approval. Following licensing to treat drooling in children for the first time, there is increasing use of both generic and proprietary GBr in practice in preference to hyoscine.

2. Underpinning research

Prevalence and significance of drooling in children with neurodevelopmental disorders

Neurodevelopmental impairments and conditions account for the highest proportion of disability in children and young people, with an estimated prevalence of 3-4%[1]. One of the most common symptoms of neurodevelopmental conditions is severe and persistent drooling. Drooling is most commonly seen in children with cerebral palsy (CP), which affects 30,000 children in the UK[2]. The rate of drooling in children with CP is around 35%, indicating that around 10,500 children with CP in the UK are affected (R2). Since drooling is commonly seen in children with other neurodevelopmental conditions, the total prevalence is much higher (for example, of the sequentially recruited children with neurodevelopmental conditions approached in R3, only 22/90 had CP). No data exist on the prevalence of drooling across all neurodevelopmental disorders, but, using these figures, an estimate for the number of children with neurodevelopmental conditions who drool is up to 90,000. Drooling is associated with skin problems, social embarrassment, damage to clothes and equipment as well as the more serious risk of aspiration leading to pneumonia. In addition, drooling increases the burden on parents and carers.

[1] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/252659/33571_2901304_CMO_Chapter_9.pdf

[2] https://thepacecentre.org/information-centre/stats-facts/

Unmet need: the lack of a licensed medication

A Newcastle-run survey of 151 paediatricians (R1) found that medication was the most common intervention for drooling in children with CP. Of the medications used, hyoscine was the most common first-line choice, and glycopyrronium bromide (GBr) the most common second line. Hyoscine has a convenient trans-dermal administration (via a patch changed every 2-3 days), whereas GBr requires oral administration 2-3 times a day. However, the lack of data on the side effects or clinical effectiveness of either medication meant that neither was licensed for treatment of drooling. A 2013 NICE evidence review[3] highlighted the lack of long-term efficacy and safety data for GBr, as well as its unlicensed status. The licensing of a drug confirms that it has been properly tested, using evidence-based systematic assessment of the quality, effectiveness and side effects.

Newcastle research comparing GBr with hyoscine

Newcastle carried out a randomised trial (R3, protocol paper R2) in 90 children comparing hyoscine to GBr. In this study, children were randomised to receive a hyoscine skin patch or GBr liquid. Dose was increased over four weeks to achieve optimum symptom control with minimal side-effects, then a steady dose was continued to 12 weeks. For both medications, the improvement in the Drooling Impact Score after four weeks was statistically and clinically significant. The five children who provided detailed feedback rated their drooling as 'good' or 'very good' and said their chin was dry and no longer sore and their clothes remained dry.

Although R3 found both medications to be effective, hyoscine was associated with more severe and frequent side effects, both predictable and non-predictable, that led to cessation of treatment. For hyoscine, 36% of parents reported a predictable side-effect that led to treatment cessation, whereas for GBr this was only 16%. For the non-predictable side-effects, 15% of parents of the hyoscine group reported adverse effects that were relatively severe, such as floppiness and seizures; whereas for GBr only one child out of 38 stopped medication, due to hyperactivity. The paper concluded that when neither medication was contraindicated or definitely preferred, GBr should be the drug of first choice.

These results subsequently informed international licensing and approval of GBr to treat drooling in children with neurodisability, and the impact of this is described below.

3. References to the research

SciVal field-weighted citation impact (FWCI) as of December 2020. Newcastle researchers in **bold.**

R1. **Parr JR**, Buswell CA, Banerjee K, Fairhurst C, Williams J, O'Hare A, **Pennington L**. (2012) Management of drooling in children: a survey of UK paediatricians' clinical practice. *Child: Care, Health and Development.* 38(2):287-91. DOI: 10.1111/j.1365-2214.2011.01213.x. FWCI: 0.63.

R2. **Parr JR**, **Weldon E**, **Pennington L**, **Steen N**, Williams J, Fairhurst C, O'Hare A, Lodh R, **Colver A**. (2014) The drooling reduction intervention trial (DRI): a single blind trial comparing the efficacy of glycopyrronium and hyoscine on drooling in children with neurodisability. *Trials.* 15:60. DOI: 10.1186/1745-6215-15-60. FWCI: 0.28.

R3. **Parr J**, **Todhunter E**, **Pennington L**, **Stocken D**, **Cadwgan J**, O'Hare AE, Tuffrey C, Williams J, **Cole M**, **Colver AF**. (2018) Drooling Reduction Intervention randomised trial (DRI): comparing the efficacy and acceptability of hyoscine patches and glycopyrronium liquid on drooling in children with neurodisability. *Archives of Disease in Childhood*. 103:371-376. DOI: 10.1136/archdischild-2017-313763. FWCI: 3.13.

4. Details of the impact

NICE recommendation of hyoscine and generic GBr

The 2017 NICE guidance NG62 (EV 1, page 262-4) recommended that both GBr and hyoscine be considered as single first-line treatments for drooling in children with CP. This guidance was

[3] https://www.nice.org.uk/advice/esuom15/chapter/Key-points-from-the-evidence

informed largely by R3, the only RCT carried out in the UK and the only one to inform "Consideration of economic benefits and harms" (page 263). The guidance noted that although hyoscine was more cost-effective than GBr, it was associated with more problematic side-effects and greater risk of treatment cessation.

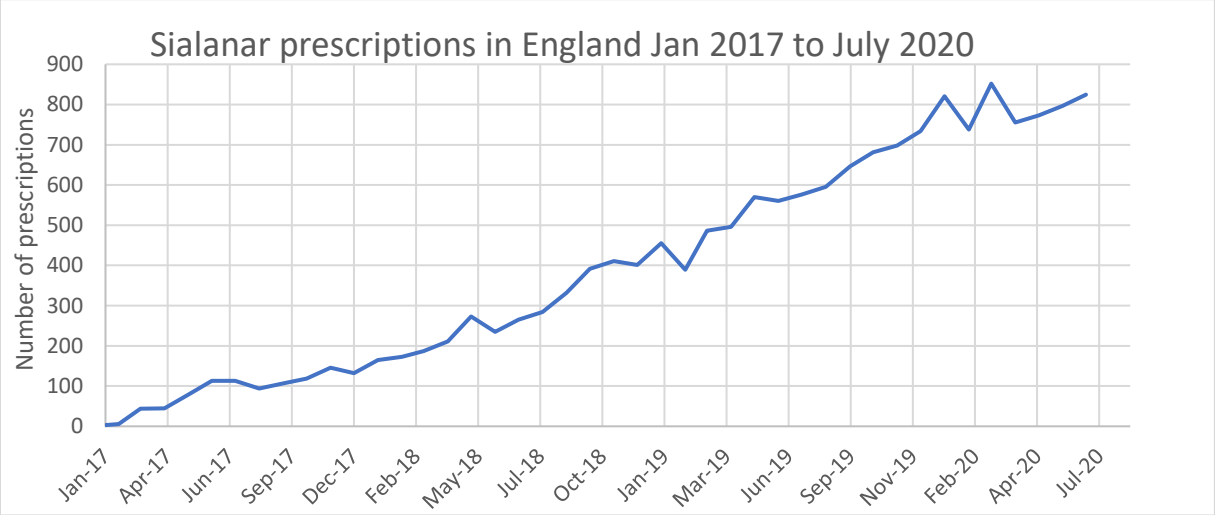
Approval of proprietary GBr across Europe

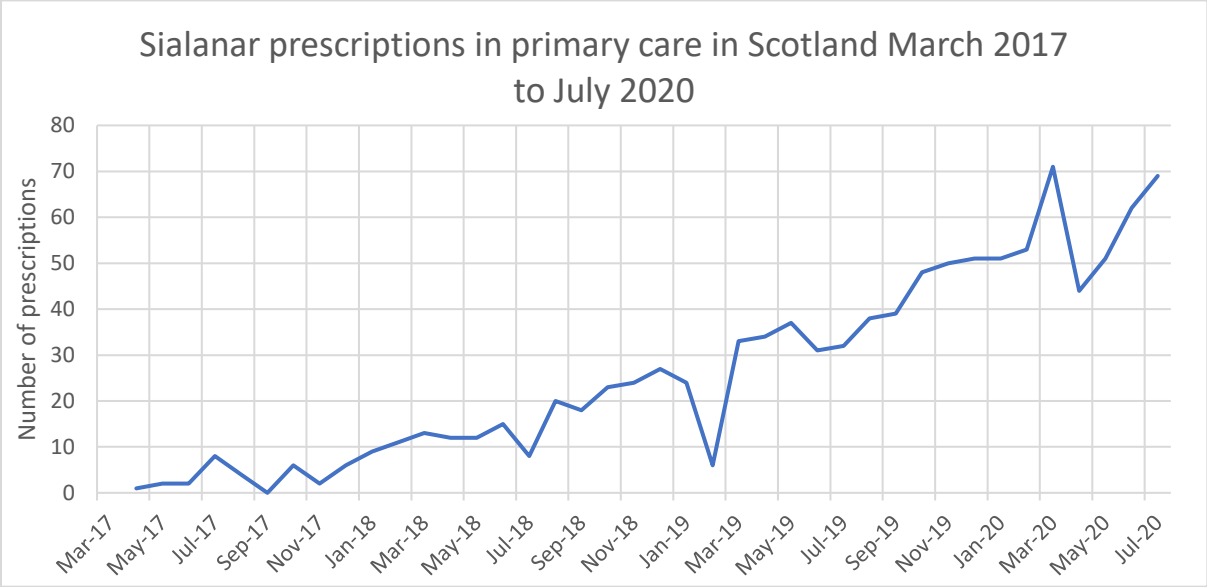
Newcastle research (R3) also informed the licensing of two proprietary GBr drugs for drooling in children with wider neurodevelopmental conditions. First, data from R3 were provided pre-publication under a confidentiality agreement to Proveca, a UK-based pharmaceutical company who manufacture the GBr drug Sialanar. These data allowed Proveca to fulfil the requirements for the European Medicines Agency (EMA) to grant a paediatric use marketing authorisation for Sialanar in September 2016 (EV2), covering all EU member states. Proveca confirmed the essential role played by Newcastle research (EV3): "Newcastle University were kind enough to share with us the results from [R3] prior to its publication. Early access to these data was essential for us to meet one of the required criteria necessary to validate the application within the strict timetable set by the EMA." Following the EMA approval, Proveca received MHRA marketing authorisation for Sialanar in the UK in September 2016 (EV4). In July 2017, the Scottish Medicines Consortium specifically approved Sialanar for use in Scotland (EV5). In April 2019, the Zorginstituut Nederland (National Health Care Institute of the Netherlands) used R3 as essential evidence in the documentation approving Sialanar for use in the Netherlands (EV3, EV6).

A second pharma company, Company A [name redacted for publication], received an MHRA additional indication for their GBr Drug A [name redacted for publication] in February 2019. This decision was largely informed by R3, as confirmed by the company (EV7): "This approval was a direct result of a body of evidence we submitted to the MHRA. This evidence included seven studies, of which [R3]… was the largest and most relevant."

Impact on number of prescriptions

Since its approval by NICE in January 2017, the number of prescriptions for Sialanar in England has increased to around 800 per month (EV8, see graph below). Sialanar is only licensed for drooling in children with neurodisability and therefore prescription numbers are a more accurate representation of use in practice than generic GBr, which is licensed for a variety of conditions. In Scotland, prescriptions in primary care have increased to around 70 a month (EV9, see graph below), and the supply of Sialanar in secondary care increased from a total of 250 ml in 2017 (approximately 21 doses) to 4,250 ml in 2019 (approximately 354 doses). Between January and July 31st 2020 alone, 4,330 ml (approximately 361 doses) was supplied (EV10). The number of prescriptions of Drug A specifically for this condition increased from 2,268 in January 2019 to 2,568 in July 2020, as confirmed by Company A (EV7).





Impact on use in practice

To investigate the preferential use of GBr over hyoscine in practice, a survey of clinicians was conducted in August 2020 and received 77 responses (EV11). Medications accounted for 58.3% of all interventions; as absolute percentages, 16.6% were GBr prescriptions (of which 9.1% Sialanar, 3.5% Drug A and 4.0% as a specially-prepared unlicensed product), and 20.7% hyoscine. The proportion of GBr prescriptions was approximately similar to the previous rate of 14.3% (of which Sialanar 7.1%, Drug A 3.6% and as a special 3.6%). However, there was a substantial fall in the prescription of hyoscine from its previous rate of 64.2%. The main reasons for changing practice were: 42.8% due to the Newcastle trial (R3), 25.7% because families prefer it, 14.2% because of guidelines from their local Trust and 8.6% due to NICE guidelines. In addition, the survey found that 23 clinicians started children on Sialanar each month. Of the children switched to Sialanar, 27.9% were switched from generic GBr and 59.5% from hyoscine. Taken together, these results show increasing use of a well-researched and licensed drug instead of either an unlicensed drug or one with greater side effects.

In summary, Newcastle research into the effectiveness and side effects of medications for drooling in children with neurodevelopmental conditions informed UK and European licensing of one generic and two proprietary drugs. As a result, international prescribing practice has changed, offering children and their parents a treatment for this distressing and potentially dangerous condition.

5. Sources to corroborate the impact

EV1. NICE guideline NG62 January 2017. https://www.nice.org.uk/guidance/ng62/evidence/full-guideline-4357166226
EV2. European Medicines Agency authorisation September 2016. https://www.ema.europa.eu/en/medicines/human/EPAR/sialanar
EV3. Letter from the Chief Medical Officer, Proveca.
EV4. Webpage on Sialanar from the Electronic Medicines Compendium. https://www.medicines.org.uk/emc/product/2301/smpc#ORIGINAL
EV5. Scottish Medicines Consortium Product Update June 2017. https://www.scottishmedicines.org.uk/media/1781/glycopyrronium_bromide_sialanar_abbreviated_final_june_2017_for_website.pdf
EV6. Zorginstituut Nederland summary assessment document (in English) April 2019 available at: https://english.zorginstituutnederland.nl/publications/reports/2019/04/09/glycopyrronium-bromide-sialanar
EV7. Letter from Company A, not publically available.

EV8. NHS England prescription information summary. Original data available from: https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data
EV9. NHS Scotland prescription information summary. Original data available from: https://www.opendata.nhs.scot/dataset/prescriptions-in-the-community
EV10. Information kindly provided by Primary Care and Prescribing Team, Public Health Scotland, available on request.
EV11. Survey data, not publically available.