Institution: King's College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Improved treatment and quality of life for patients with overactive bladder syndrome through developing new ways of administering Botulinum Toxin–A

1. Summary of the impact

King's College London (KCL) researchers contributed to the discovery that increased C fibre nerve activity in the bladder is a major cause of overactive bladder (OAB) syndrome. Based on this insight, KCL researcher Professor Dasgupta, a surgical urologist at Guy's Hospital, and his team pioneered a new surgical technique for micro-injecting Botulinum Toxin-A (BTX-A) directly into the bladder to suppress C fibres and improve bladder control. The KCL team then conducted the world's first successful clinical trials into the minimally invasive injection of BTX-A in OAB patients. These trials received significant international media coverage. This cost-effective OAB therapy is now licensed by the EU and FDA, is recommended in national and international guidelines, and has significantly improved the treatment of a common health problem.

2. Underpinning research

The issues of overactive bladder syndrome: Overactive bladder (OAB) syndrome is a major health problem affecting approximately 1 in 6 people. In the UK alone, this translates to 5 million affected individuals. OAB syndrome significantly reduces people's quality of life and is a burden in daily living. Unfortunately, a large proportion of patients suffer in silence as current treatment options are often inadequate.

KCL researchers contribute to identification of the molecular mechanisms responsible for overactive bladder syndrome: In 2005, KCL researcher Professor Dasgupta (Guy's Hospital, 2002-present) along with colleagues at University College London and Imperial College London identified that certain receptors within C nerve fibres in the bladder were present at abnormal levels in OAB syndrome (1). These proteins could be targeted and suppressed using Botulinum Toxin-A (BTX-A). A model describing how BTX-A affected the bladder to control overactivity was therefore proposed and published by the combined team in the journal European Urology, where it remains one of the top five cited papers in this field (2).

KCL clinicians pioneer a new surgical technique to improve BTX-A injections: In 2005, researchers at King's College London led by Professor Dasgupta (in collaboration with University College surgeon Professor Fowler) pioneered the use of a minimalistic surgical technique to introduce BTX-A into the bladder under local anaesthetic, removing the need for an overnight hospital stay (3). This became known as the **"**Dasgupta technique". KCL researchers further demonstrated that this surgical approach could effectively treat all types of OAB syndrome (4).

Original KCL research leads to clinical trials in OAB patients: In 2007, the functional urology team at KCL (led by Professor Dasgupta in collaboration with pharmaceutical partners Allergan, Inc.) conducted the first randomised double-blind clinical trial – treating 34 OAB patients with BTX-A injections. These studies demonstrated a substantial benefit of treatment – reducing both incontinence and how often and how urgently patients had to urinate (5). Their subsequent research in 2008 demonstrated that such BTX-A therapies acted quickly, improving symptoms within four days in OAB patients who had previously failed to respond to conventional treatments (6).

In 2011, the KCL team led an extended clinical trial recruiting over 300 patients across multiple countries – including the USA, Canada, Germany and the UK. Similar significant improvements in bladder control were observed following BTX-A therapy in the OAB patients (7).

KCL collaborative research continues to uncover new targets for the treatment of OAB syndrome: Current KCL research by Professor Dasgupta and Dr Smith (Guy's Hospital, 2007-present), in collaboration with the European INCOMB group and pharmaceutical partner Adprotech Ltd., continues to further our understanding of how BTX-A improves bladder performance, leading to the development of better ways to deliver such drugs.

KCL-developed therapies are clinically useful for other diseases involving bladder dysfunction: In 2007, KCL researchers analysed the ability of the BTX-A micro-injection technique to improve bladder dysfunction associated with other diseases. More than 40 multiple sclerosis (MS) patients suffering severe bladder incontinence were recruited and treated with BTX-A using the Dasgupta technique. Results showed an extremely significant positive impact on patients' quality of life, and substantial improvements in bladder function (8).

KCL researchers also highlighted evidence that BTX-A treatment could be useful for the treatment of benign prostatic hyperplasia (BPH), where an enlarged prostate gland is often associated with bladder incontinence (9).

3. References to the research

1) Apostolidis A, Popat R, Yiangou Y, Cockayne D, Ford AP, Davis JB, **Dasgupta P**, Fowler CJ, Anand P. Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. *J Urology*. 2005;174:977-83.

2) Apostolidis A, **Dasgupta P**, Fowler CJ. Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. *Eur Urol*. 2006;49:644-50.

3) Apostolidis A Dasgupta R, Fowler CJ, **Dasgupta P**. A minimally invasive technique for outpatient local anaesthetic administration of intradetrusor botulinum toxin in intractable detrusor overactivity. *BJU Int.* 2005;96:917-8.

4) Popat R, Apostolidis A, Kalsi V, Gonzales G, Fowler CJ, **Dasgupta P**. A comparison between the response of patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity to the first intradetrusor injection of botulinum-A toxin. *J Urol.* 2005;174:984-9.

5) Sahai A, Khan MS, **Dasgupta P**. Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo controlled trial. *J Urol.* 2007;177:2231-6.

6) Kalsi V, Apostolidis A, Gonzales G, Elneil S, **Dasgupta P**, Fowler CJ. Early effect on the overactive bladder symptoms following botulinum neurotoxin type A injections for detrusor overactivity. *Eur Urol.* 2008;54:181-7.

7) Rovner E, Kennelly M, Schulte-Baukloh H, Zhou J, Haag-Molkenteller C, **Dasgupta P**. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. *Neurourol Urodyn.* 2011;30:556-62.

8) Kalsi V, Gonzales G, Popat R, Apostolidis A, Elneil S, **Dasgupta P**, Fowler CJ. Botulinum injections for the treatment of bladder symptoms of multiple sclerosis. *Ann Neurol.* 2007;62:452-7.

9) Goldstraw MA, Kirby RS, **Dasgupta P**. The role of botulinum toxin in benign prostatic hyperplasia. *BJU Int.* 2006;98:1147-48.

Since 2002, the KCL research programme into improving outcomes in OAB patients has been awarded substantial charitable and industrial funding. This includes major grants from:

- Multiple Sclerosis Society. 4-year grant (2003-2007) **£198,000**
- British Urological Foundation. 1-year grant (2005-2006) **£35,000**

- Allergan, Inc. investigator and educational grants (2003-2014) **£239,000**

4. Details of the impact

Improved patient outcomes and quality of life through BTX-A administration using the Dasgupta technique: KCL research has changed the way that OAB syndrome is managed by using a less invasive BTX-A bladder-injection technique that rapidly reduces overactive bladder symptoms and removes the need for major reconstructive surgery to increase bladder capacity. Using validated clinical questionnaires, patients undergoing BTX-A treatment show significant improvements in their quality of life, as they are able to overcome negative emotions and social limitations associated with the syndrome, and experience fewer physical symptoms (10).

Enhanced cost effectiveness using BTX-A injections as a treatment for OAB syndrome: A comparison of the more invasive surgical therapy for OAB syndrome, augmentation cystoplasty, with BTX-A micro-injections has shown that the BTX-A approach is cheaper over a 5-year period (11). Given the minimally invasive nature of BTX-A therapy, these lower costs are often directly related to the decreased incidence of surgical complications. The high success rate of BTX-A treatment also reduces the need for additional costly complementary treatments, such as incontinence aids or antibiotics for urinary-tract infections.

International uptake of the Dasgupta surgical technique through KCL-based teaching & mentorship programmes: The KCL-pioneered minimally invasive BTX-A injection technique has been taught by the KCL team to more than 60 colleagues from around the world, including the UK, Italy, India, South Africa, the USA, Switzerland, the Netherlands and Belgium (12).

Incorporation of KCL-developed BTX-A therapies into national and international clinical guidelines: KCL research has had a significant impact on informing the clinical management of OAB patients around the world. KCL research (see [1] - [8] above) has informed the treatment of lower urinary-tract disorders in NICE guidelines (13) and EU consensus panels (14). This research has been further incorporated into international guidelines established by the Canadian Urological Association (15) and the American Urological Association (16).

KCL-developed BTX-A therapies are approved by the FDA and the EU: In 2012, the EU recommended the approval of BTX-A for OAB treatment (17). In January 2013, the FDA approved the use of BTX-A for OAB (18). These approvals substantially extend the reach of this new therapy.

KCL researchers invited to advise on development of further innovations: As a result of Professor Dasgupta's discoveries and experience with BTX-A treatment, he has been invited to join the advisory boards of several companies actively developing new surgical innovations and drugs. Examples include Allergan Inc., Intuitive Surgical, Pfizer and Astellas (2008-2013).

Coverage of KCL research by international media: The exciting impact of KCL's research (see [5] above) into OAB syndrome has been featured by many media news outlets. This has included national coverage by BBC Radio 4 and the Daily Mail, and international coverage from the Alpha Galileo Foundation, Nursing Times and the Times of India (24).

5. Sources to corroborate the impact

10) Sahai A, Dowson C, Khan MS, **Dasgupta P**. Improvement in quality of life after botulinum toxin-A injections for idiopathic detrusor overactivity: results from a randomized double-blind placebo-controlled trial. *BJU Int*. 2009;103:1509-15.

11) Padmanabhan P, Scarpero HM, Milam DF, Dmochowski RR, Penson DF. Five-year cost analysis of intra-detrusor injection of botulinum toxin type A and augmentation cystoplasty for refractory neurogenic detrusor activity. *World J Urol.* 2011:29:51-7.

12) Visiting surgeons who have learned and been mentored in the Dasgupta technique: p.88-92 http://www.theprostatecentre.com/m/4e687c502abaa/file

Governmental and professional bodies using KCL research to formulate treatment guidelines:

13) NICE guidelines for Urinary incontinence in women: the management of urinary incontinence in women, 2nd edition 2013 *Cites ref 5 above*. http://www.nice.org.uk/nicemedia/live/13019/62658/62658.pdf

14) Apostolidis A, Dasgupta P, Denys P, Elneil S, Fowler CJ, Giannantoni A, Karsenty G, Schulte-Baukloh H, Schurch B, Wyndaele JJ, European Consensus Panel. Recommendations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: a European consensus report. *Eur Urol*. 2009;55:100-19. *Cites refs 1-6 and 8 above.*

15) Bettez M, Tu Le M, Carlson K, Corcos J, Gajewski J, Jolivet M, Bailly G. 2012 Update: Guidelines for adult urinary incontinence collaborative consensus document for the Canadian Urological Association. *Can Urol Assoc J.* 2012:6:354-63. *Cites ref 7 above.* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3478335/pdf/cuaj-5-354.pdf

16) Gormley EA, Lightner DJ, Burgio KL, Chai TC, Clemens Q, Culkin DJ, Das AK, Foster HEF Jr, Scarpero HM, Tessier CD, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guidelines. *J Urol.* 2012;188 (6 suppl):2455-63. *Cites ref 5 above.*

17) EU approval, UK Medicines Information website http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=5585

18) FDA press release, Jan 18, 2013 http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm336101.htm

Media coverage of KCL research:

24) Media coverage:

- BBC Radio 4 http://www.bbc.co.uk/radio4/science/casenotes_tr_20080826.shtml
- The Daily Mail http://www.dailymail.co.uk/health/article-1192234/How-Botox-jabs-help-iron-weak-bladder-problems.html
- The Alpha Galileo Foundation http://www.alphagalileo.org/ViewItem.aspx?ItemId=58452&CultureCode=en
- The Nursing Times http://www.nursingtimes.net/nursing-practice/clinical-zones/continence/botox-could-help-women-with-weak-bladders/5042638.article#
- The Times of India http://articles.timesofindia.indiatimes.com/2009-10-04/beauty/28100627_1_injections-bladder-placebo