Institution: King's College London		
Unit of Assessment: UoA1		
Title of case study: Improved long-term quality of life of patients with overactive bladder syndrome with Botulinum Toxin–A bladder injections		
Period when the underpinning research was undertaken: 2002 – 2020		
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:**
Prokar Dasgupta	Professor of Surgery	2002 – present
Arun Sahai	Consultant Urological Surgeon & Reader	2007 – 2020
Period when the claimed impact occurred: 2015 – 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Overactive bladder (OAB) affects 8,000,000 people in the UK alone. King's College London conducted the first clinical trials involving a new surgical technique for micro-injecting Botulinum Toxin-A (BTX-A) directly into the bladder to suppress C fibres and improve bladder control. Compared to other treatments for overactive bladder, BTX-A therapy is more cost-effective and less invasive. The beneficial effect to the patient is maintained for over 20 years. This therapy has been recommended in NICE guidelines and international clinical guidelines. Through the guidelines and King's-based teaching and mentorship programmes, BTX-A therapies developed at King's have improved the quality of life of millions of people around the world.

2. Underpinning research

The issues of overactive bladder syndrome: Overactive bladder (OAB) syndrome is the name for a group of urinary symptoms in which the main one is a frequent feeling of needing to urinate to a degree that it negatively affects a person's life. It is a major health problem affecting approximately 1 in 6 people including around 8,000,000 affected individuals in the UK alone, making OAB more prevalent than asthma and diabetes combined. It is driven by nerves called C-fibres, which King's researchers found to be exquisitely sensitive to toxins including Botulinum Toxin-A (BTX-A).

King's researchers contribute to identification of the molecular mechanisms responsible for overactive bladder syndrome: The King's team along with colleagues at Queen Square Institute of Neurology, identified that certain protein receptors within C nerve fibres in the bladder, such as P2X3 and TRPV1, were overexpressed in OAB syndrome. These nerve receptors are responsible for sending signals that activate the detrusor muscle, which is a smooth muscle found in the wall of the bladder. It remains relaxed to allow the bladder to store urine, and contracts during urination to release urine. The bladder of people with OAB contracts suddenly and repeatedly without the person having control and when it's not full, giving the sensation that they must go to the bathroom urgently and too much. King's researchers found that these proteins could be targeted and suppressed using BTX-A. An injection of BTX-A in the detrusor muscle has an important direct effect on the motor function of the urinary bladder, and an indirect effect on the sensory regulation of bladder function. BTX-A inhibits the most important excitatory neurotransmitter in the bladder. This helps the muscle relax and allows an individual more time to get to the bathroom when they feel the need to urinate. This mechanism was proposed in the journal European Urology **(1)**, where it remains one of the top five cited papers in this field.

King's clinicians pioneer a new surgical technique to improve BTX-A injections: King's researchers pioneered the use of a minimally invasive surgical technique to introduce BTX-A into the bladder under local anesthetic, removing the need for an overnight hospital stay. The technique has become known as the "*Dasgupta technique*" and it takes about 15 minutes to complete. Researchers at King's demonstrated that using a dose of 100-200 units of BTX-A could effectively treat all symptoms of OAB **(1, 2)**.

Clinical trials in OAB patients: In collaboration with pharmaceutical partners Allergan Inc, the team at King's conducted the first randomised double-blind clinical trial of BTX-A therapy for OAB due to idiopathic detrusor overactivity, treating 34 patients with BTX-A injections. These studies demonstrated a substantial benefit of treatment – reducing both incontinence and how often and urgently patients had to urinate **(2)**. King's subsequent research 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. Following this, the King's 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 these patients. King's researchers then reported the medium to long-term effectiveness and safety of BTX-A injections in OAB **(3)** using Patient Reported Experience Measures (PREMs). These are psychometrically validated tools (e.g. questionnaires) used to capture patients' interactions and the degree to which their needs are being met. They showed consistent high quality of life scores and satisfaction rates, up to 90%, across treatment cycles **(3)**.

Overall patient satisfaction with the dedicated BTX-A service offered was high and showed that it can result in a more positive patient experience **(4)**. The use of PREMs are advocated in order to fully capture the patient's views of the quality of services and treatments they receive. As a result, BTX-A has had widespread clinical uptake and is an important treatment option in many OAB patients.

3. References to the research

1. 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. doi: 10.1016/j.eururo.2005.12.010.

2. 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. doi: 10.1016/j.juro.2007.01.130.

3. Eldred-Evans D, **Sahai A**. Medium- to long-term outcomes of botulinum toxin A for idiopathic overactive bladder. *Ther Adv Urol.* 2017 Jan;9(1):3-10. doi: 10.1177/1756287216672180.

4. Malde S, Dowson C, Fraser O, Watkins J, Khan MS, **Dasgupta P, Sahai A**. Patient experience and satisfaction with Onabotulinumtoxin A for refractory overactive bladder. *BJU Int.* 2015 Sep;116(3):443-9. doi: 10.1111/bju.13025.

4. Details of the impact

OAB is not a normal part of ageing. It is a health problem that can persist for many years if it is not treated, and can negatively affect people's lives. King's research has enabled the treatment for OAB to progress substantially and, as a consequence, positively impact the lives of people who suffer from this condition.

King's improved patient outcomes and quality of life through BTX-A administration using the Dasgupta technique: King's research has involved 3000 patients over 20 years and 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, King's work has provided measurable improvements to the lives of thousands of patients. Using validated patient reported experience measures (PREMs) such as Client Satisfaction Questionnaire-8, patients undergoing BTX-A treatment show significant improvements in their quality of life, such as overcoming negative emotions and social limitations and experiencing fewer physical symptoms associated with urinary incontinence **(A)**. The beneficial effect can be maintained over 20 years without adversely affecting the bladder due to repeated injections. Evidenced by the PREMS, the BTX-A treatment received an overall patient satisfaction score of 28.3 out of 32 **(A)**. In 2019, The Urology Foundation reported that the method developed by King's researchers transformed the lives of patients through the UK's first dedicated Botox clinic at Guy's Hospital **(B)**. The clinic currently injects close to 200 patients each year **(B)**.

Enhanced cost effectiveness using BTX-A injections as a treatment for OAB syndrome: A 2018 US study comparing different methods for treating OAB syndrome over a 10-year period demonstrated BTX-A to be the treatment that produced the largest gain in Quality Adjusted Life Years – QALYs (7.179) and lowest estimated incremental cost–effectiveness ratio (ICER) (USD32,680/QALY) of all assessed treatments compared with Best Supportive Care (BSC) **(C)**. The Markov model used in the comparison study confirmed that the treatment with BTX-A 100 Units was the most cost-effective compared to BSC and all other methods **(C)**. Given the minimally invasive nature of BTX-A therapy, these lower costs are often directly related to the decreased incidence of surgical complications **(C)**.

Treatment	ICER (USD per QALY)
BTX-A	USD32,680
Sacral Nerve Stimulation Devices	USD288,096
Percutaneous Tibial Nerve Stimulation	USD71,126
Mirabegron (25 mg)	USD794,395

Incorporation of King's-developed BTX-A therapies into national and international clinical guidelines: King's research has had a significant impact on informing the clinical management of OAB patients around the world. It has informed the treatment of lower urinary-tract disorders in NICE guidelines 2019 **(D)**. This research has been further incorporated into international guidelines established by the European Association of Urology (EAU) 2019 **(E)** and the American Urological Association (AUA) 2019 **(F)**.

International uptake of the Dasgupta surgical technique through King's-based teaching & mentorship programmes: The King's pioneered minimally invasive BTX-A injection technique has been taught by the King's team to colleagues from around the world (2014-2015), including the UK, Italy, India, South Africa, the USA, Switzerland, the Netherlands and Belgium. A

Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, London **(G)** stated that Dasgupta has been *"leading pioneering research into the overactive bladder for well over 25 years. His seminal contributions to the field include developing the technique of injecting botulinum toxin into the bladder wall under local anaesthesia. This minimally invasive "Dasgupta technique" has become an internationally accepted standard, and Prokar has personally trained 62 colleagues in the United Kingdom and overseas across the specialties of Urology and Urogynaecology […] The impact of his research has been substantial and has influenced the practice of Urology both nationally and world-wide."*

5. Sources to corroborate the impact

(A) PREMS (PDF): Malde S, Dowson C, Fraser O, Watkins J, Khan MS, **Dasgupta P, Sahai A**. Patient experience and satisfaction with Onabotulinumtoxin A for refractory overactive bladder. *BJU Int.* 2015 Sep;116(3):443-9. doi: 10.1111/bju.13025.

(B) TUF Matters (PDF): News and Views from The Urology Foundation. Issue 09, 2019 [pages 10-11]

(C) 2018 Comparative study showing BTA-X injections to have largest QALYs over ten-year period: Murray B, Hessami SH, Gultyaev D, Lister J, Dmochowski R, Gillard KK, Stanisic S, Tung A, Boer R, and Kaplan S. Cost–effectiveness of overactive bladder treatments: from the US payer perspective. Journal of Comparative Effectiveness Research 2019 8:1, 61-71(https://www.futuremedicine.com/doi/full/10.2217/cer-2018-0079)

(D) NICE Guidance: Urinary incontinence and pelvic organ prolapse in women: management, 2019 [page 21] (https://www.nice.org.uk/guidance/ng123/resources/urinary-incontinence-and-pelvic-organ-prolapse-in-women-management-pdf-66141657205189)

(E) EAU Guidelines: Urinary incontinence, 2019 [reference 61] (https://uroweb.org/guideline/urinary-incontinence/)

(F) Diagnosis and Treatment of Non-Neurogenic Overactive Bladder (OAB) in Adults: an AUA/SUFU Guideline (2019) [references 171, 190 and 191] (https://www.auanet.org/guidelines/overactive-bladder-(oab)-guideline)

(G) Testimonial (PDF): Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, London.