UNIVERSITY OF BIRMINGHAM

Horizon Scanning Centre

New and emerging technologies for urinary and faecal incontinence

January 2014

NHS
National Institute for Health Research

This report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

The NIHR Horizon Scanning Centre,
University of Birmingham, United Kingdom
nihrhsc@contacts.bham.ac.uk
http://www.hsc.nihr.ac.uk/

CONTENTS

EXECUTIVE SUMMARY

This review aimed to identify new and emerging health technologies, including drugs, medical devices and procedures, for the diagnosis, monitoring and management of urinary incontinence (UI) and faecal incontinence (FI) in both men and women.

Faecal and urinary incontinence are underreported conditions that can have a significant impact on quality of life. People with incontinence may be treated by a wide range of health professionals according to a range of care pathways. Continuing to develop the evidence base for current treatment options and improving access to incontinence services are central to improving incontinence care.

Searching of bibliographic databases, clinical trial registries, technology databases and other online sources was combined with company contacting and consultation with a range of clinical experts to identify relevant new and emerging health technologies. Clinical experts and a patient led organisation were then asked to review the identified technologies and provide comment on innovation, current usage, potential impact (on patient outcomes and NHS resources) and potential barriers to adoption of these technologies. The Bladder and Bowel Foundation provided valuable insights into the technologies presented from a patient and carer view.

A wide range of technologies were identified, many of which represent incremental developments of current technologies, such as improvements in the selectivity or delivery of antimuscarinic agents and the evolution of synthetic slings, injectable bulking agents and artificial sphincters. In total, twenty-three new and emerging technologies for incontinence were identified: two for diagnosis, six pharmacological therapies and 15 other therapeutic technologies.

Bladder diaries are central to the diagnosis and assessment of urinary incontinence, and newer electronic versions may improve the reliability and accuracy of data, and improve self-care. Patients would welcome developments that make diaries more user-friendly and easier to fit into busy lives.

Currently there are a limited range of pharmacological options for UI in both men and women. Antimuscarinic agents are the most common drug treatment option for urge UI and overactive bladder (OAB), however they may not be tolerated due to side effects such as, dry mouth, blurred vision, constipation and urinary retention. The Bladder and Bowel Foundation expressed particular concern that patients could not always access newer licensed therapies due to their relative cost when compared to older agents; and that wider benefits on quality of life need to be considered when determining the cost effectiveness of these agents. Ongoing research into biomarkers and improving understanding of the pathophysiology of incontinence is likely to lead to new drug developments, and this review identified novel compounds which may offer alternative treatment options in the future.

There are no licensed drugs for FI at present. The review identified one compound which may offer an inexpensive treatment option in the future. Many with mixed urinary and faecal incontinence state that FI has a bigger effect upon their dignity and ability to lead a normal life. Patients would welcome more cohesive services and access to effective drug treatments for FI.

Synthetic sling technologies have seen significant incremental developments. They are well established for use in female stress incontinence and have seen more recent expansion for male stress incontinence. This review identified one sling being trialled for FI. Concerns expressed by clinical experts and patients about mesh erosion following pelvic organ prolapse repair surgery may limit further development and adoption of these technologies.

Clinical experts were particularly interested in the potential of regenerative medicine in the future treatment of both urinary and faecal incontinence. These technologies advance on current injectable bulking agents and may provide an alternative to sling repair in the future. However, patients are currently sceptical about these technologies and their potential for complications.

Minor out-patient based procedures for incontinence, such as Lyrette™ transurethral SUI system, Solace Balloon Delivery System™ and Surinate® Bladder Management System, appeared to be novel, though experts were sceptical about their potential efficacy.

Most of the technologies identified in this review are at an early stage of development. Further well designed trials and the collection of cost effectiveness data are required before these can be considered for adoption in clinical practice.

ACKNOWLEDGEMENTS

Internal review team

Dr Jane Fowles, Public Health Specialist Registrar
Dr Kristina Routh, Clinical Senior Lecturer and Medical Advisor
Dr Derek Ward, Co-Director and Medical Advisor
Dr Sue Simpson, Associate Director

Clinical expert advisors

Nine clinical experts contributed to the review and the NIHR Horizon Scanning Centre wishes to thank them for their valuable input. See Appendix 1 for statements of conflicts of interest.

- Mr Zaki Almallah, Consultant Urologist, University Hospital Birmingham NHS Foundation Trust
- Mr Mark Chapman, Consultant Colorectal Surgery, Heart of England NHS Foundation Trust
- Professor Christopher Chapple, Consultant Urological Surgeon, Royal Hallamshire Hospital, Honorary Senior Lecturer of Urology, University of Sheffield, Visiting Professor of Urology, Sheffield Hallam University
- Professor Alan Cottenden, Professor of Incontinence Technology, University College London.
- Mr Marcus Drake, Consultant Urological Surgeon, Southmead Hospital, visiting Professor, University of the West of England, Senior Lecturer, University of Bristol
- Ms Karen Nugent, Consultant Colorectal Surgeon, Southampton General Hospital and University of Southampton
- Mr Nikesh Thiruchevalm, Consultant Urological Surgeon, Cambridge University Hospitals NHS Foundation Trust
- Professor Douglas Tincello, Professor of Urogynaecology, University of Leicester
- Mr Philip Toozs-Hobson, Consultant Obstetrician and Gynaecologist, Birmingham Women's NHS Foundation Trust

Patient group involvement

The Bladder and Bowel Foundation reviewed this document and collated patient views on individual technologies, providing a valuable insight into those identified. The NIHR Horizon Scanning Centre would like to thank the Bladder and Bowel Foundation for their valuable input.
http://www.bladderandbowelfoundation.org/

1. INTRODUCTION AND BACKGROUND

This review focuses on new and emerging technologies for the diagnosis, monitoring and management of both faecal and urinary incontinence. These conditions have different causes, care pathways and treatment options available, therefore the definitions, current management options and identified technologies have been separated into sections on female urinary, male urinary and faecal incontinence.

1.1 CLINICAL NEED AND BURDEN OF DISEASE

1.1.1 FEMALE URINARY INCONTINENCE

Urinary incontinence (UI) in women is defined as 'involuntary urinary leakage' and classified into the following symptom groups:

- Stress UI – leakage of urine after coughing, exercise, etc.
- Urge UI or overactive bladder (OAB) – leakage of urine associated with a strong urge to urinate.
- Mixed UI – a combination of stress and urge UI.[1]

Management is targeted towards the predominant symptom.

Incontinence may be significantly underreported as women may delay seeking help due to embarrassment or the belief that it is a normal consequence of childbirth or the ageing process. The Leicestershire MRC Incontinence Study found that 34.2% of women reported incontinence at times; 3.5% on a daily basis, 11.8% weekly, 7.3% monthly and 11.6% yearly. The prevalence of incontinence increases with age. While stress UI is most common, women aged over 60 years show an increase in urge and mixed UI and are more likely to report moderate to severe symptoms.

Incontinence has a wide range of risk factors including age, obstetric history, menopause and obesity. It is a distressing and socially disruptive condition which may lead to individuals avoiding wider social opportunities. It poses significant costs to individuals, carers and health and social care services[2].

1.1.2 MALE URINARY INCONTINENCE

Lower urinary tract symptoms (LUTS) in men comprise a range of symptoms which reflect the complex anatomical relationships between the bladder, urethra and prostate:

- Storage symptoms – frequency, nocturia, urgency and incontinence.
- Voiding symptoms – slow stream, spraying, intermittent/hesitant flow, terminal dribble.
- Post micturition symptoms – incomplete emptying and dribble.

Although NICE guidance tackles these symptoms as a group, this review focusses primarily on storage symptoms. NICE suggest that 90% of men aged 50-80 years suffer from bothersome LUTS; while voiding problems are the most common, storage symptoms are the most bothersome[3]. Incontinence is associated with increasing age

due to bladder overactivity and the consequences of prostatic surgery. Storage symptoms are estimated to affect 42% of those over 75 years of age[3].

Management and technologies for voiding and post micturition symptoms are outside the scope of this review.

1.1.3 FAECAL INCONTINENCE

Faecal incontinence is the involuntary loss of solid or liquid stool and can be classified by symptoms (urge or passive soiling), nature of leakage (solid, liquid, mucus or flatus), patient group and underlying cause (following childbirth, neurological injury or disease, or following colorectal/anal surgery, etc.). People with faecal incontinence may be treated by a wide range of health professionals and it has been considered a neglected health care problem in the UK, often overshadowed by urinary incontinence. NICE estimate that 1-10% of adults may be affected and that 0.5-1% of adults experience regular faecal incontinence which impacts on their quality of life. Embarrassment, stigma and fear of physical symptoms can have far reaching impacts on quality of life and restrict daily activities[4].

1.2 CLINICAL GUIDELINES

The current care pathways for investigation and management of both urinary and faecal incontinence are well described in the following guidelines:

NICE clinical guideline. Urinary incontinence in women (CG171). September 2013[2].
NICE clinical guideline. Lower urinary tract symptoms (CG97). May 2010[3].
NICE clinical guideline. Faecal incontinence (CG49). June 2007[4].

A brief outline of current care is provided throughout this report to help place new developments in context. Where technologies outside this guidance are described, relevant interventional procedure guidance or technology appraisals are referenced.

1.3 RELEVANT INCONTINENCE PROJECTS IN THE UK

The James Lind Alliance (JLA)

The JLA facilitate priority setting partnerships (PSPs), bringing together patients, carers and clinicians to identify and prioritise current treatment uncertainties in key topic areas. A PSP to identify the top 10 treatment uncertainties for urinary incontinence was formed in 2006, completing work in 2008. The uncertainties generated centre on better understanding the evidence for current approaches rather than identifying areas of need that could be addressed by new technologies.

Health Technology Cooperatives (HTC)

Devices for dignity have a urinary continence management theme addressing the diagnosis, treatment and management of bladder dysfunction. One of their projects is

described in this report. Enteric is the bowel function HTC, however no technologies for faecal incontinence developed by this group were identified.

The Bladder and Bowel Foundation (B&BF)

The B&BF are a UK wide charity formed in 2008 providing information and support to individuals affected by incontinence and their families, carers and healthcare professionals.

National Institute for Health Research

The NIHR fund a wide range of research programmes in the field of incontinence.

1.4 AIMS AND OBJECTIVES

The aim of this review was to identify new and emerging technologies, including drugs, medical devices and procedures, for the diagnosis, monitoring and management of urinary and faecal incontinence in men and women.

The purpose of this work is to provide information to healthcare policy makers, commissioners, clinicians and patient groups about new technologies that may be of relevance in the future of incontinence management. This report, which has been informed by consultation with clinical experts, is not intended to provide a complete overview of all technologies for incontinence but summarises key areas of innovation.

2. METHODS

We sought to identify new and emerging technologies for the diagnosis, monitoring and management of urinary and faecal incontinence by systematically searching a range of sources, including:

- Technology databases – NIHR HSC (internal database), Pharmaprojects, Adis Insight, EuroScan International Network.
- Bibliographic databases – Medline, Embase and Cochrane
- Clinical trial registries – clinicaltrials.gov
- Relevant journals and conference reports suggested by experts
- Medical technology news websites e.g. Clinica

These sources were supplemented by a general internet search. Experts from the field of incontinence were invited to contribute to the review and asked to provide information on new and emerging technologies known to them.

Searches were targeted towards technologies meeting the following criteria:

- Pharmaceuticals in phase II or III clinical trials (ideally estimated to be within 24 months of licensing)
- Medical device and diagnostic (MedTech) technologies that are:
    - ‘emerging’ – expected to be CE marked or launched in the UK in the next 24 months
    - ‘new’ – CE marked and in the launch or early post-marketing stages

- ‘new and poorly adopted’

Identified technologies were investigated further by contacting developers for information on availability and UK licensing plans. In many cases limited information was available and/or provided. Those confirmed to no longer be in active development were excluded.

Technologies presented in this review are either confirmed to be in active development or have no up to date information available. Many of the technologies presented are not likely to be licensed or launched in the next 24 months.

Technologies were reviewed by clinical experts and the B&BF, who provided comment on innovation, current availability, possible impacts on patient outcomes and NHS systems and resources and barriers to wider adoption.

Results are grouped into technologies for diagnosis and conservative management, pharmacological treatment and therapeutic technologies for both urinary and faecal incontinence.

3. DIAGNOSIS AND CONSERVATIVE MANAGEMENT OF INCONTINENCE

The initial diagnosis and conservative management of incontinence is described below. There is a general trend towards making diagnostic technologies and biofeedback devices smaller and more portable. Most recent developments centre on electronic devices or apps for use as bladder diaries.

3.1 URINARY INCONTINENCE

3.1.1 FEMALE URINARY INCONTINENCE – CURRENT APPROACHES

The initial assessment and management of UI may take place in both primary and secondary care. History and examination help to identify precipitating factors, exclude other diagnoses and then categorise into stress, urge/OAB or mixed UI. Initial diagnosis is assisted by the use of bladder diaries and incontinence specific quality of life scales. Conservative management includes urinalysis to exclude infection and lifestyle advice, such as weight loss (for high body mass index, BMI), modified fluid intake and caffeine reduction. Further management depends on the type of incontinence:

- **Stress UI** – 3 month trial of supervised pelvic floor muscle training (PFMT). Home exercise programmes can be continued if beneficial. Electrostimulation and/or biofeedback can be used to aid adherence/motivation in those who cannot actively contract the pelvic floor.
- **Urge UI** – 6 week bladder training programme. Pharmacological treatment can be started in primary care (see Section 4).
- **Mixed UI** – either/both of the above depending on the predominant symptom.

Where further input is needed women can be referred to the secondary care multidisciplinary team (MDT).

Urodynamics (multi-channel filling and voiding cystometry) can be used to assess women thought to have overactive bladder due to detrusor overactivity (involuntary contraction of the bladder muscle during filling), voiding dysfunction or previous surgery for stress incontinence. If diagnosis is still unclear, ambulatory or videourodynamics can be used. Women can then be advised on further therapeutic options including, pharmacological and invasive approaches or no further treatment, depending on the risks, benefits and personal preferences[2].

3.1.2 MALE URINARY INCONTINENCE – CURRENT APPROACHES

Initial assessment of male LUTS is similar to that of female UI. History, examination and urinalysis are used to identify precipitating causes, exclude other diagnoses and classify into storage, voiding or post micturition symptoms. Initial diagnosis is assisted by bladder diaries and validated symptom scores. Initial management consists of lifestyle advice e.g. modifying fluid intake. Conservative management depends on the nature of storage symptoms:

- **Overactive bladder** – supervised bladder training.
- **Stress UI** (usually secondary to prostatic surgery, especially radical surgery, for benign or malignant disease) – 3 month trial of supervised pelvic floor muscle training. Electrostimulation and/or biofeedback may be offered, though the clinical and cost effectiveness is unclear.

Where conservative management fails men may be offered pharmacological treatment or surgery. Multichannel cystometry can be offered to those men considering invasive treatment options[3].

3.1.3 CHANGING APPROACHES

Developing bladder diaries

Bladder diaries form the mainstay of diagnosis and monitoring for incontinence, and can be used to collect a range of information about urinary frequency and incontinence episodes. Current guidance recommends the use of bladder diaries in initial assessment for a minimum of 3 days, covering work and leisure time. Most centres use paper versions with some centres having access to formats that can be scanned for computer analysis. Accessible, user-friendly electronic forms could improve completion by patients and interpretation by healthcare professionals. Two novel electronic versions are described below.

Devices for Dignity are an NIHR Healthcare Technology Cooperative (HTC). They are developing an electronic bladder diary which is about to be trialled in the community. It is a hand held, touch screen device for patient use, allowing them to record time, volume passed and desire to urinate. It is based around NICE guidance and is intended to interface directly with the clinician's computer or transmit data via email.

Clinical expert opinion: *Experts said that paper versions are often incorrectly or inadequately completed, a novel electronic gadget may encourage patients to complete a true record and provide accurate data. Electronic diaries would need to be integrated efficiently into hospital/clinical systems to prove successful. Experts were concerned about the costs associated with investment in hardware.*

Bladder and Bowel Foundation opinion: *Patient views echo the lack of compliance with traditional paper bladder diaries, often stating that life is simply too busy and that completing the diary gets forgotten. Recently B&BF were involved in a trial testing electronic diaries. Feedback confirmed greater interest but failed to provide consistent results. Those taking part, particularly men, did not like carrying a measuring jug around with them. It was suggested that the diary should be incorporated into an app rather than forming an additional piece of kit to carry around. Carers also reported that bladder diaries can be very difficult to achieve with dementia sufferers and other vulnerable groups.*

Three Ten LLC have developed the iDry app, a free iPhone app for urinary incontinence. It enables users to track incontinence events and progress in response to interventions. It has had 900 downloads since launch in November 2012, 61 of which were in the UK.

Clinical expert opinion: *Experts had not come across patients using this app, but thought it may be helpful in self-help or primary care. Although a simple free app may be helpful, many patients are elderly and may struggle with this technology. Ethical considerations around data security would need to be considered.*

Bladder and Bowel Foundation opinion: *We recently hosted a patient workshop at which the general feeling was that apps were suitable for a growing number of incontinence sufferers, but that traditional methods of recording may need to be maintained for those who did not have access to technology. An app linked to intervention may be advantageous as a tool for carers to monitor symptoms and flag concerns related to vulnerable groups.*

Biomarkers

Biomarkers are used to measure risk factors, diagnose disease and assess severity, progression and response to treatment. The search for clinically meaningful biomarkers is an active research topic in most disease areas. A range of biomarkers are being investigated for incontinence, including; neurotrophins (such as urinary nerve derived growth factor, urinary brain derived growth factor), prostaglandins, urinary cytokines and genetic markers[5]. Most research activity is aimed at better understanding the pathophysiology of incontinence and identifying novel therapeutic targets. The clinical value of these biomarkers is still unclear.

3.2 FAECAL INCONTINENCE

The initial management and care of faecal incontinence begins in primary care. Baseline assessment should include medical history, examination (including anorectal examination) and cognitive assessment where appropriate, and aim to identify or exclude; faecal loading, prolapse, lower gastrointestinal cancers, anal sphincter injury and neurological conditions. Initial conservative interventions include; bowel habit training, diet and fluid intake advice and toilet access arrangements. Empirical anti-diarrhoeal treatment can be started in primary care.

Where further input is needed patients can be referred to specialist continence services. Specialist conservative treatment options have limited evidence, but include:

- Supervised pelvic floor muscle training +/- biofeedback.
- Electrical stimulation.
- Rectal irrigation.

If these measures are unsuccessful then further assessment to determine anorectal anatomy and function should be considered. These include:

- Anorectal physiology.
- Endoanal ultrasound (US) (if unavailable then MRI, endovaginal US or perineal US).
- Proctography[4].

3.2.1 CHANGING APPROACHES

A range of different imaging modalities and devices have been explored for faecal incontinence. Technological developments focus on improving portability. No novel technologies were identified.

4. PHARMACOLOGICAL THERAPY FOR INCONTINENCE

Pharmacological approaches to urinary and faecal incontinence differ. There are no licensed drug treatments for faecal incontinence and one drug for stress urinary incontinence. Drugs for OAB are more established although still limited to two licensed drug classes. A range of novel drugs have been trialled but many have not progressed beyond phase II trials. New technologies for urinary incontinence are not separated into male and female groups as final licensing indications may vary from the gender profiles of current trials.

4.1 URINARY INCONTINENCE

4.1.1 FEMALE URINARY INCONTINENCE

Urge UI/OAB

Pharmacological treatment for OAB or mixed UI with predominant urge symptoms can be started in primary care. Current first line options include antimuscarinic agents such as:

- Oxybutynin (immediate release)[i].
- Tolterodine (immediate release).
- Darifenacin (once daily).

Women should be reviewed after 4 weeks to monitor outcomes and side effects, such as dry mouth or constipation. Where first treatment is ineffective or poorly tolerated due to side effects, options include another antimuscarinic agent from the list above or;

- Trospium (immediate release).
- Oxybutynin (extended release).

Where antimuscarinics are contraindicated, ineffective or have unacceptable side effects, mirabegron, a first in class beta-3-adrenoreceptor agonist (licensed in the UK in early 2013), offers another treatment option[6]. Where pharmacological options fail or are poorly tolerated women should be referred for consideration of invasive treatment.

Stress UI – invasive therapies are considered the current best treatment option for stress UI not responding to conservative therapy. However duloxetine (a serotonin-norepinephrine reuptake inhibitor - SNRI) may be offered as second line treatment for stress UI if women are not suitable for surgery or express a preference for drug treatment.

Other drug treatments include desmopressin to reduce nocturia and intravaginal oestrogens in postmenopausal women with vaginal atrophy and OAB[2].

4.1.2 MALE URINARY INCONTINENCE

Where conservative management fails, men may be offered pharmacological treatment depending on symptom type:

- Voiding LUTS – alpha blockers (alfuzosin, doxazosin, tamsulosin or terazosin), or 5-alpha reductase inhibitors for those with prostate enlargement.
- OAB – anticholinergics (choice depending on tolerance of side effects) or mirabegron.

Loop diuretics or desmopressin can be offered for those with nocturnal polyuria[3].

4.1.3 CHANGING APPROACHES

There are a limited range of pharmacological options for UI in both men and women. Antimuscarinics are the most common drug treatment option for urge UI/OAB, however may not be tolerated due to side effects, such as, dry mouth, blurred vision, constipation and urinary retention. Mirabegron, the first beta-3-adrenoreceptor agonist offers an additional treatment option for OAB where antimuscarinics are poor tolerated, contraindicated or ineffective. This section highlights some of the incremental developments in these drug classes.

[i] Except frail elderly

Selectivity of antimuscarinics

There are a range of selective antimuscarinics in development, intended to deliver improved efficacy or side effect profiles. Plethora Solutions is developing PSD 506, an orally active M2 and M3 muscarinic receptor antagonist, this has been in phase II UK trials for OAB in women, male LUTS and neurogenic bladder. No further information on current development is available. SALVAT is developing tarafenacin, an orally active M3 receptor antagonist, which has been in phase II EU trials, though no recent EU development has been reported, active development continues under license to Kwang Dong Pharma in South Korea. Kyorin Pharma have licensed imidafenacin, an orally selective M1 and M3 antagonist, now commercially available in Japan, it has been in phase I UK trials, although no recent development has been reported.

Clinical expert opinion: *These products will have been developed to try and improve efficacy or side effect profile compared to existing drugs in the class. Side effects are a known complication of antimuscarinic drugs and it seems unlikely that any new formulation will be dramatically better than the drugs on the market. Would need to show significant benefit and equivalent cost in an already crowded market.*

Bladder and Bowel Foundation opinion: *There are mixed views regarding efficacy and long term compliance of antimuscarinic therapy. The reviewed NICE guidance for the management of urinary incontinence (2013) revisited first line treatments and made recommendations based on cost-effectiveness, and this may be related to this increasing number of calls we receive reporting poor tolerance of first line antimuscarinics. Oxybutynin was already known for poor compliance as a direct result of the intolerable side effects. Patients feel strongly that they are being denied more tolerable medications due to cost considerations.*

Delivery of antimuscarinics

Antimuscarinics are currently available in oral, sublingual and transdermal preparations. Two companies have been developing vaginal delivery systems for a currently available antimuscarinic oxybutynin. TEVA had been developing DR3001, a silicone based ring system in phase III US and phase II trials in Germany, though development has now been discontinued. FemmePharma is developing FP1097, using their patented PARDEL (pelvic and reproductive delivery system). This has completed phase II US trials, though no further development is reported.

Clinical expert opinion: *Most experts felt that transdermal oxybutynin has shown reasonable efficacy and reduced side effects compared to oral agents. Some experts felt that results from transdermal patches had proved disappointing and their uptake limited due to patient preference and local reactions. While it is likely that the vaginal route would provide a therapeutic effect, experts felt more information on absorption and efficacy compared to oral agents was needed. Some experts questioned whether vaginal products would be acceptable to women in the UK and may lead to other local side effects such as vaginal dryness.*

Bladder and Bowel Foundation opinion: *Patient opinion on transdermal patches is mixed.*

Combining agonist with antagonist

TheraVida Inc is developing combination products for incontinence. The company's claim to novelty resides in their platform technology allowing a combination of agonist with antagonist in one therapeutic product offering opportunities to counteract known side effects. The company have a range of products in development for OAB and urge UI, the majority of which are in proof of concept studies. They have two products in phase II trials with phase III studies planned. Both are combinations of the antimuscarinic tolterodine with modified release pilocarpine (muscarinic agonist); THVD-201 is a twice daily preparation and THVD-202 is a once daily preparation.

Clinical expert opinion: *Most experts felt that this was an interesting and novel concept. With the wide range of antimuscarinics currently available, experts felt that improved clinical and cost effectiveness would need to be demonstrated if it was to prove competitive. Cost would be a key barrier to adoption in the NHS. Some experts felt that current data suggest efficacy and discontinuation rates were not significantly different to that of current treatments.*

Additional beta-3-adrenergic agonists

Following on from the recent launch of mirabegron, Merck Sharp & Dohme Ltd are developing another beta-3-adrenoreceptor agonist MK-4618, which is currently in phase II trials in Europe. Kissei have been developing KUC-7483 or ritobegron. This has been in phase III trials in Japan and phase II trials in Europe, though no recent development has been reported.

Clinical expert opinion: *As mirabegron is proving successful in clinical practice in terms of side effects, patient acceptance and efficacy, new products would need to demonstrate at least similar clinical and cost effectiveness. Adding more competition to the market is interesting.*

Bladder and Bowel Foundation opinion: *Mirabegron has been well received by a number of patients. However there are still many patients who have failed previous antimuscarinic therapy and are not necessarily aware of this new drug. Often those who fail on a treatment assume that there isn't an alternative. This was highlighted at a patient opinion workshop recently. The B&BF helpline, continence services and GPs need to ensure that those who may benefit from this medication are aware of it.*

4.1.4 NOVEL TECHNOLOGIES

While the technologies described above represent incremental adjustments on current technologies, some novel agents for urinary incontinence are being developed. Early scoping identified many novel agents in phase II trials, however many of these have discontinued active development for incontinence. The technologies described below are those where development is confirmed to be ongoing or no further information is available.

Dexmecamylamine (TC5214)

Targacept are developing dexmecamylamine (TC5214), an orally active nicotinic channel modulator acting on receptors in the bladder, intended for OAB in males and females. It is currently in phase II trials in the US with an estimated primary completion date of September 2014.

Clinical expert opinion: *This is a novel therapy approach, acting on the sympathetic pathways to reduce bladder contractility. If shown to be effective it could represent a new class of drug for OAB, which could be combined with anticholinergics. The same issues of clinical and cost effectiveness compared to antimuscarinics and mirabegron, will determine if this is adopted by the NHS. One expert queried whether this may also work for faecal incontinence.*

Cizolirtine (E-4018)

Esteve have been developing cizolirtine (E-4018) for urge UI/OAB. Cizolirtine is an orally active dimethylaminopyrazole, which modulates substance P and calcitonin gene-related peptide release. It has been in phase II/III trials for urge and stress UI in the EU, however the UK arm of trials was ended prematurely[7]. No further development information is available.

Clinical expert opinion: *This is a novel therapy approach. Most experts felt that the mechanism of action fits current understanding of OAB, however could not see a pharmacological reason for efficacy in stress UI. One expert was concerned about previous problems with calcium channel blockade. More evaluation of clinical and cost effectiveness would be needed for it to compete with current drug choices.*

ONO-8539

ONO have been developing ONO-8539 an orally active prostaglandin e receptor-1 antagonist for OAB. It has completed phase II trials in the EU and Russia in both males and females. No further information is available.

Clinical expert opinion: *Most experts felt that this was an interesting idea. One expert stated that 'prostaglandins are involved in bladder contraction so the concept makes pharmacological sense. It would be a new agent with a unique mode of action so may be more likely to find a market niche since there would be no direct competitors, but cost issues would still be relevant'.*

UISH-001

Beech Tree Labs have been developing UISH-001, a fixed dose combination product for sublingual use in female UI. The company claim it is composed of 'two molecules, both well-known but not previously used for this indication', however no further information on mechanism of action is available. It has been in phase II trials in the US,

and the company report that results are in favour of the treatment (report posted on clinicaltrials.gov). No further information is available.

Clinical expert opinion: *The results from the clinicaltrials.gov webpage show no difference to placebo. Not able to comment of the drugs themselves, but given the lack of effect this is unlikely to be marketed.*

PSD-503 for stress incontinence

Plethora Solutions is developing PSD-503, a topical gel alpha agonist (phenylephrine) applied to the vaginal wall at the level of the internal sphincter to the external urethral meatus. It is thought to improve urethral tone while avoiding systemic side effects. It has been in phase II EU trials (although the UK arm was reported to be terminated).

Clinical expert opinion: *Most experts felt that oral alpha agonists had proved to be ineffective and intolerable and were sceptical that vaginal application would be effective. One expert stated that topical alpha blockers had been in phase II trials for years, and doubted this would be a major player. Another felt that 'duloxetine as a licensed drug with a reasonable profile hasn't proved successful and surgery has such good results'. One expert felt this may prove useful in some circumstances if the clinical effectiveness of as required (PRN) application could be demonstrated.*
Bladder and Bowel Foundation opinion: *All novel therapies offer hope to sufferers of incontinence. Patients with urinary and/or faecal incontinence are commonly heard stating that 'they will try anything'. They are also increasingly frustrated when seemingly effective treatments are deemed unobtainable as a result of poor cost effectiveness.*

4.2 FAECAL INCONTINENCE

There are currently no pharmacological therapies specifically licensed for faecal incontinence. Many medications prescribed for other conditions may have side effects on gut motility or stool consistency, patients with faecal incontinence should have a medication review to minimise these side effects. Loperamide or codeine phosphate can be used as anti-diarrhoeals either regularly or as required for faecal incontinence before further referral. Laxatives can also be used to promote complete rectal emptying[4].

Bladder and Bowel Foundation opinion: *Patients report that the lack of cohesive services and drug treatments compound the effects of faecal incontinence on quality of life. Many with mixed urinary and faecal incontinence state that faecal incontinence has a bigger effect upon their dignity and ability to lead a normal life.*

4.2.1 CHANGING APPROACHES

There are currently no drug treatments specifically licensed for faecal incontinence. Current NICE guidance refer to clinical trials of phenylephrine to enhance sphincter tone in FI, however there was no significant evidence of effect although numbers were small. Phenylephrine is not currently licensed for FI. If compounds are found to be clinically effective for FI they could have a significant impact on patient care.

4.2.2 NOVEL TECHNOLOGIES

Methoxamine rectal (NRL001)

Norgine are developing NRL001 a methoxamine hydrochloride wax suppository intended for once daily administration. It is thought to reduce faecal incontinence episodes and severity by improving the tone of the internal anal sphincter. Phase II trials are currently recruiting in the UK/EU.

Clinical expert opinion: *One expert felt that the mechanism of action suggests that this may improve resting pressure and passive incontinence in some patients; however the clinical effects may be minimal. Another felt that a number of topical preparations had been trialled for FI, and if this approach was shown to be effective the potential market is large. Another felt there were few inexpensive options to treat these patients so this could potentially have a small but significant role.*

Bladder and Bowel Foundation opinion: *Patients would argue that decisions should not be purely based on cost alone. Hidden costs to society should be considered such as improvements in quality of life or enabling an individual to return to work.*

5. THERAPEUTIC TECHNOLOGIES AND SURGERY FOR INCONTINENCE

There are a wide range of invasive technology options for the treatment of both urinary and faecal incontinence. Some of these are well established technology groups, though incremental developments can still be identified. Some technology groups are gender specific while others may be applicable to both sexes.

Current treatment approaches for male and female urinary incontinence have been described separately. New approaches to current technology groups and novel technologies are described where most relevant.

5.1 FEMALE URINARY INCONTINENCE

Stress UI

Where conservative management fails, women can be offered more invasive interventions. Current recommended options include:

- Synthetic mid-urethral tapes:
    - ‘bottom-up’ retropubic approach using TVT™ (tension free vaginal tape) or Advantage™.
    - ‘inside-out’ transobturator approach using TVTO™ (TVT Obturator).
    - ‘outside-in’ transobturator approach using Obtape, Monarc™ or Obtryx™ Halo.
- Open colposuspension (laparoscopic approaches are not routinely recommended).
- Autologous rectus fascial slings.
- Intramural bulking agents – these can be considered although are not as effective as synthetic tapes and repeat injections may be needed.
- Artificial urinary sphincter – only if previous surgery has failed.

Urge UI/OAB

Where conservative and pharmacological interventions have been unsuccessful or poorly tolerated the following invasive interventions may be considered:

- Botulinum toxin A bladder wall injection – only where women are willing and able to perform intermittent catheterisation.
- Sacral nerve stimulation (SNS) – for women unsuitable for, or not responding to botulinum toxin A.
- Percutaneous posterior tibial nerve stimulation (PTNS) – not routinely recommended and only used where women do not want botulinum toxin A or SNS.
- Augmentation cystoplasty, if able to self-catheterise.
- Urinary diversion – only where all the above are unsuitable[2].

5.1.1 CHANGING APPROACHES

This section summarises some of the incremental developments and expansion of established technology groups for female urinary incontinence that are well covered in current guidance.

Evolution of female slings

Surgical procedures for stress incontinence aim to provide tension free support to the midurethra or bladder neck. On straining or coughing this comes under tension, slightly obstructing the urethra.

Sling procedures and devices differ according to:

- Tissues to which they are fixed – pubic arch or rectus sheath.
- Route of insertion:
    - Open – abdominal or combined abdomino-vaginal.
    - Minimally invasive – retropubic approach (bottom up or top down), obturator approach (outside in or inside out).
- Materials – synthetic (type dependent on pore sizes), woven, biological.

Mid urethral synthetic slings appeared in the mid-1990’s and are currently the most common surgical procedure for stress incontinence, overtaking open colposuspension

and autologous rectus fascial slings. They offer a minimally invasive alternative to previous open surgical techniques, with improved recovery and shorter hospital stays. However this is balanced by complications such as mesh erosion. In January 2012, to better understand the safety and effectiveness profile, the US Food and Drug Administration (FDA) ordered post market surveillance studies for mesh slings for stress UI and meshes used for pelvic organ prolapse repair. Meshes used for pelvic organ prolapse repair are regarded as at a higher risk of erosion complications than devices used for stress UI.

A range of sling devices have been developed and are in widespread usage, however some devices have been withdrawn following the FDA's concerns[8]. In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) continue to gather information on adverse events associated with slings[9].

Currently recommended sling approaches and devices for stress UI are described in section 5.1 above, and are confined to Type 1 macroporous polypropylene tapes with high quality evidence of efficacy and safety. Newer developments include a range of single incision slings (tapes inserted via a single vaginal incision); however these are not currently recommended outside of research use[10].

Evolution of injectable bulking agents

Injectable bulking agents are used in both urinary and faecal incontinence. A range of biological and synthetic products have been developed for injection including; autologous fat, silicone, hyaluronic acid/dextranomer copolymer, carbon coated zirconium beads, polytetrafluoroethylene and hydroxylapatite. Injection routes include the transurethral approach using a cystoscope or through the skin parallel to the urethra. Bulking agents are less effective than slings and, repeat injections may be needed to achieve efficacy, which may diminish over time[11]. Current guidance for stress UI in women recommends the use of silicone, carbon coated zirconium beads or hyaluronic acid/dextrancopolymer bulking agents. Injectable bulking agents can also be used for stress UI in males however local scarring following prostate surgery may limit efficacy. Regenerative medicine technologies are in development for use in incontinence and hope to provide a single injection sustained bulking effect (see section 5.1.2).

Evolution of neurostimulation

Neurostimulation is the electrical stimulation of nervous tissue to produce a therapeutic effect. Neurostimulation for incontinence has been used as a treatment and as an adjunct to pelvic floor muscle training. Usage varies by nerve targeted (sacral or posterior tibial) and device type (implantable, percutaneous or transcutaneous). It is an approach that has been used in both urinary and faecal incontinence.

Current guidance for OAB recommends sacral nerve stimulation or percutaneous posterior tibial nerve stimulation only. Sacral nerve stimulation is currently delivered as a two-step procedure; a trial of percutaneous sacral nerve stimulation using a lead placed alongside the sacral nerve prior to implantation of the stimulator device (InterStim®, Medtronic). Implanted devices may encounter problems with lead migration and explantation. Percutaneous posterior tibial nerve stimulation is an out-patient procedure involving a needle placed next to the tibial nerve and a surface electrode on

the foot. Treatment usually consists of 12 x 30 minute sessions (Urgent® PC, Uroplasty)[12]. Transcutaneous electrical nerve stimulation (TENS) devices are widely available, and use electrodes placed on the skin with controller units varying in portability. TENS devices have been widely used particularly for labour pain, and are not currently recommended for treatment of urinary incontinence.

Johnson and Johnson have developed a portable transcutaneous sacral nerve stimulator (VERV™) intended for patient use in OAB. It consists of a patch which sits on the lower back and a remote controller. The NIHR Horizon Scanning Centre has completed a briefing for VERV™. It was CE marked in 2010. Geko™ from Firstkind Ltd takes this principle further and is being trialled for faecal incontinence (see section 5.3.2).

5.1.2 NOVEL TECHNOLOGIES

Regenerative medicine (SUI)

Regenerative medicine and cellular therapy is a rapidly developing field that is being investigated as a treatment option for a wide range of diseases. A number of companies are developing autologous muscle derived cells for the treatment of stress incontinence. Muscle biopsies are taken from the patient (often from thigh muscle), samples are then returned to the lab for cell extraction and expansion. Muscle precursor cells are isolated and frozen for injection. Cells are then injected into the external sphincter, usually by transurethral ultrasound guided injection. Administration protocols vary by technology and trial and most participants are female. The injections are thought to add bulk and regenerate sphincter muscle, thereby reducing symptoms of stress UI, and are intended to be one off treatments.

- Cooke MyoSite is developing AMDC-USR (autologous muscle derived cells for urinary sphincter repair), which is in phase III trials in the UK/EU and Canada (also in phase I trials for faecal incontinence).
- Innovacell Biotechnologie is developing ICES13 for female stress incontinence for application with their proprietary injectors, it is in phase III trials in the UK and EU. The NIHR Horizon Scanning Centre has produced a briefing for ICES13.
- HRA Pharma and their subsidiary Celegos are developing RCD1 which has completed phase I/II trials, the company are currently focussing on development for faecal incontinence.

Clinical expert opinion: *Experts have been aware of early work in the area for some time. One expert stated 'This is one of the few truly novel ideas. If it works it has the potential to alter the treatment landscape quite considerably, though it depends how effective and how minimal the surgery is'. Most experts felt that the technology would have to compete with current TVT surgery in terms of clinical and cost effectiveness. One expert felt that this technology potentially lacked the significant complications associated with current surgical approaches, such as voiding difficulty and tape erosions. Another raised uncertainties about ideal placement of the injections. Most experts had concerns about the potential cost and cited this as a key barrier to NHS adoption.*

Bladder and Bowel Foundation opinion: *In the wake of the mesh investigations a growing number of female patients are sceptical about this type of procedure and the potential for complications such as pain, sexual dysfunction etc.*

Lyrette™ transurethral SUI system (Renessa Micro-remodelling system)

Verathon Medical UK Ltd has developed Lyrette™ transurethral system for female stress UI. It uses controlled, low-power, non-ablative radiofrequency energy to heat small submucosal sites in the bladder neck and proximal urethra, resulting in localised thermal collagen remodelling. Upon healing the treated area is less compliant and more resistant to involuntary leaks. It is intended to improve continence without affecting normal urination. A single treatment application takes approximately 10 minutes. Patients may experience an immediate improvement in symptoms due to localised swelling, followed by a period of leaking as swelling subsides. Collagen remodelling occurs later and patients may have to wait 60-90 days to see durable improvement. Lyrette™ is already available in the US and is likely to come to the UK for clinical and research use. A similar technology, Secca® from Mederi Therapeutics Inc, is currently available for treatment of faecal incontinence.

Clinical expert opinion: *Expert opinion was mixed. Some experts felt that similar technologies and radioablative techniques had been around for a while and proved disappointing. Concerns were raised about lack of efficacy and the risk of stenosis following the procedure. Some experts felt this was a novel and simple technique which may have potential if proven to be clinically effective with few significant side effects. As it appears to be an out-patient procedure, it would avoid the need for and costs of in-patient care.*

Solace Balloon Delivery System™ (AttenueX) - SUI

Solace Therapeutics has developed the Solace Balloon Delivery System™ or AttenueX as a novel approach to the treatment of female stress UI. It is a small lightweight device that floats in the urinary bladder and is intended to act as a 'shock absorber', reducing or eliminating involuntary leakage, when intra-abdominal pressure is raised. It is inserted via cystoscopy, and in trials the device has been replaced every 90 days. It is CE marked however there is no further information on UK availability. Clinical trials are underway in the EU (60 patients - estimated primary completion date December 2013) and US (166 female patients).

Clinical expert opinion: *Most experts thought this was an interesting and novel technology, though most were sceptical about its effectiveness, agreeing it was only likely to work in those with mild stress UI symptoms. Good clinical and cost effectiveness would have to be demonstrated. Experts raised concerns about having a foreign body in the bladder and problems with encrustation and infection. One expert thought UK patients were unlikely to accept the intervention and another was concerned it would be too expensive for adoption.*

Senrebotase (AGN214878) for OAB – male and female

Bladder wall injections of botulinum toxin A is one current treatment option for OAB. Allergan are developing senrebotase as an alternative bladder injectable. It is a recombinant clostridial neurotoxin protease which selectively delivers endopeptidase to cleave SNARE proteins, thereby inhibiting neurotransmitter release. It is intended for

use in OAB in both males and females, and is currently in phase II trials in the EU and US.

Clinical expert opinion: *Most experts were interested in a new injectable as an alternative to botulinum toxin A. Given the success of botulinum toxin A, there would have to be robust evidence of clinical and cost effectiveness for this to be adopted in the NHS. Most felt this was of interest for the future however one expert was wary about the potential for wider adoption given current geographical variation in the availability of botulinum toxin.*

Bladder and Bowel Foundation opinion: *Some patients report being dissatisfied following botulinum toxin A injections, as they consequently have to perform intermittent self catheterisation. Many find this daunting initially, and most would benefit from being better counselled on the practicalities beforehand.*

5.2 MALE URINARY INCONTINENCE

Where conservative and pharmacological management fail, men with storage LUTS may be offered more invasive options, depending on symptom type.

OAB and detrusor overactivity:

- Botulinum toxin A bladder wall injections – if able to self-catheterise.
- Implanted sacral nerve stimulation (SNS) - if responsive to a trial of percutaneous SNS.
- Cystoplasty – only for those willing and able to self-catheterise.

Stress UI (interventions usually offered as part a randomised controlled trial only):

- Injection of intramural bulking agents.
- Male slings.
- Implanted adjustable compression devices.
- Artificial sphincters.

Urinary diversion may be offered where symptoms have not responded to conservative or drug treatments, and if cystoplasty or sacral nerve stimulation are not appropriate or acceptable[3].

5.2.1 CHANGING APPROACHES

Prostate surgery

Male stress incontinence is usually secondary to prostate surgery, either for benign or malignant disease. Improving the treatment of voiding symptoms in male LUTS has a significant role to play in reducing the prevalence of male urinary incontinence. Transurethral resection of the prostate (TURP) has been the mainstay of treatment for benign disease. A range of less invasive treatment options are now available Technologies for improving prostate surgery are outside the scope of this review.

Male slings

Male slings are a developing technology group offering an alternative to the artificial urinary sphincter. They act by either compressing the urethra or providing bulbar urethral or retrobulbar tissue support. Like female slings, approaches and devices vary by materials used, surgical approach (retropubic or transobturator) and tissues to which they are fixed. A range of devices are available, though they are less well established than female slings, and are usually recommended only for use as part of a randomised controlled trial. Current devices include InVance™ (AMS), a polypropylene tape bone anchored sling, Advance™ (AMS), a transobturator polypropylene tape, and I-STOP® TOMS® (CL Medical) a four arm polypropylene sling. Newer developments include adjustable slings, including, Argus™ (Promedon) and Male Remeex™ System (Neomedic), which allow the tension on slings to be adjusted after surgery[13].

Implants and artificial urinary sphincters

Artificial urinary sphincters have been available since the 1970's and have been used for both male and female stress incontinence. The most well established device is AMS800™ (American Medical Systems), consisting of a cuff placed around the bulbous urethra or bladder neck, a pressure regulating balloon/fluid reservoir, and a control pump sited in the scrotum (or labia when used in females). Mechanical problems, such as leaks, fluid loss, or pump obstruction can occur, which incremental adjustments to the design have attempted to address. Other adverse events include infection, cuff erosion and urethral atrophy.

Alternatives to AMS800™ are available and have mainly been used in male stress incontinence. FlowSecure™ was CE marked in 2012, and is another occlusive cuff device, premoulded as one unit and intended to reduce mechanical failure by leakage. The device allows pressure adjustments *in situ* after implantation and is meant to be more responsive to changes in intraabdominal pressure. While designed for male incontinence, the device cuff sizes could accommodate the female bladder neck. Zephyr ZSI 375 is an alternative CE marked moulded occlusive cuff and pressure regulating tank, which can be adjusted by injection or removal of fluid[12].

Uromedica have developed partially occlusive devices for both male (Pro-ACT™) and female (ACT®) incontinence. Both devices consist of two balloons implanted either side of the bladder neck which are inflated to improve continence and can be adjusted as necessary[14]. Section 5.2.2 describes indwelling urethral valves as an alternative to implanted devices for male UI.

5.2.2 NOVEL TECHNOLOGIES

Some of the technologies described in section 5.1.2 may be relevant to male incontinence. Senrebotase has been trialled in males with OAB and regenerative medicine approaches with autologous muscle cells may be suitable for men with stress UI, although the majority of trials are in women.

Two additional technologies were identified at differing stages of development that are intended to act as non-surgical urethral valves. These could be seen as part of the artificial sphincter family described above.

Surinate® Bladder Management system

Urovalve are developing Surinate® for male urinary incontinence. It is a catheter device loaded onto an inserter. Insertion is similar to that of an indwelling catheter. The inserter disengages leaving Surinate *in situ*, passing from the bladder to approximately half way down the urethra. A magnetically controlled valve at the distal end enables closure and bladder filling while maintaining continence. A hand held magnet placed near the scrotum regulates opening and closing and allow urine to flow. It offers a no cut alternative to artificial sphincters with no external protrusion, leads or collecting devices. It has been trialled in 19 men with further trials planned, in clinical trials the device has remained in place for up to 30 days.

Clinical expert opinion: *Most experts felt that similar technologies had been developed as concepts but had failed as trials progressed, due to adverse events and costs. They were concerned about stone formation, tissue erosion and migration risk, encrustation, infection and difficulties of retrieval. Some felt it may offer advantages over catheters and valves however this would depend on the frequency and ease of insertion or change and the safety profile. Most felt this was unlikely to be widely adopted.*

Assureflow

This is an academic development (designed by Angelene Ozolins) and follows the same underlying principle as Surinate but with a very different approach. It is unlikely to be commercialised in the near future, but has attracted interest from developers. It is presented as an interesting contrast in approach and demonstrates growing interest in nanotechnology and shape memory alloys. It is a valve that sits in the urethra, operated using a hand held device. The valve is made of three concentric stent like tubes. The inner tubes are made of Nitinol, an alloy that changes shape in response to temperature and stress. The composition of the alloy can be varied to have different thresholds of elasticity. Normal body temperature causes the outer tube to stiffen and close providing continence. A hand held actuator uses inductive heat to stiffen the inner tube forcing the outer tube open allowing urine to flow. Once the actuator is removed the inner tube softens and the outer tube stiffens restoring continence. The actuator has a USB port to enable voiding pattern information storage and transfer.

Clinical expert opinion: *Experts had similar reservations to those expressed about Surinate.*

5.3 FAECAL INCONTINENCE

Where conservative options are not successful, invasive interventions can be considered. Current options include:

- Surgical sphincter repair – patients with full length external anal sphincter defects.
- Internal anal sphincter repair – either through surgical repair, the injection of bulking agents or application of thermal injury (Secca®).

- Sacral nerve stimulation (SNS) – following evaluation of response to percutaneous SNS in patients who are not suitable for sphincter repair.
- Neosphincters – patients where SNS trials have been unsuccessful may be offered:
    - Stimulated graciloplasty.
    - Artificial anal sphincter.
- Stoma formation – where all other options have been considered[4].

5.3.1 CHANGING APPROACHES

Bulking agents

Like urinary incontinence there are a range of injectable materials available for faecal incontinence, including synthetic and biological products. A range of injection techniques have been proposed but the ideal method of injection is unclear. Most injectables have problems with infection, migration and need for repeat treatment. Optimal agents should be non-biodegradable, non-reactive, non-migratory and easy to inject. Newer agents are designed around these characteristics[15]. Novel developments include regenerative medicine to combat the need for repeat injections and the implant Gatekeeper™, described in section 5.3.2.

Evolution of neurostimulation

See section 5.1.1 for more information.

Current guidance recommends sacral nerve stimulation for treatment of faecal incontinence. Neurostimulation devices have shown shifts towards increasing portability and patient use. Geko™, described below, further develops on the portability and ease of use of current technologies.

Neosphincters

There are two current approaches to neosphincters for faecal incontinence: implantable devices and surgical modification by stimulated graciloplasty, the creation of a new sphincter using transposed gracilis muscle connected to a pulse generator implanted in the abdominal wall[16]. A magnet is used to disrupt the generator signals to allow voiding.

American Medical Systems adapted their artificial urinary sphincter to create the Acticon™ Neosphincter in the mid 1990's. It is an implanted device consisting of an occlusive cuff placed round the anal canal, a pressure regulating balloon and a control pump sited in the labia or scrotum. Squeezing the pump allows voiding of stool, fluid then transfers back to the cuff restoring continence. Anal sphincters have seen less development than artificial urinary sphincters, though FENIX® (described below) represents a novel approach to the implantable sphincter.

5.3.2 NOVEL TECHNOLOGIES

Regenerative medicine

See section 5.1.2 for further technology details.

Three companies are developing autologous muscle cell therapies for injection into the anal sphincter to treat faecal incontinence:

- HRA Pharma is developing RCD2 which is in phase II trials in the EU with plans for phase III trials.
- Innovacell Biotechnologie is developing ICEF15 which is in phase II/III trials.
- Cooke MyoSite is developing AMDC (autologous muscle derived cells), which is in phase I/II trials.

Clinical expert opinion: *Experts felt this was an interesting concept and might reduce infection rates. However there may still be issues with migration and infection associated with any perianal injectable. New technologies will need to demonstrate comparable clinical and cost effectiveness to other injectables if they are to be adopted in the NHS.*

Bladder and Bowel Foundation opinion: *It is imperative that new technologies do not inflict further damage e.g. erosion. At a recent patient workshop, a number of people spoke about failed treatments and the negative psychological effect that this had on them.*

Gatekeeper™

THD Labs have developed Gatekeeper™ an alternative to current bulking agents for faecal incontinence. It is a bulking prosthesis in the form of a thin, solid, polyacrylonitrile cylinder that thickens and shortens within 24 hours of implantation. Four prostheses are implanted in the intersphincteric space under endoanal US guidance. It is intended to be a single treatment with sustained efficacy compared to other injectable bulking agents. It was CE marked in 2010 and has been used in over 50 patients in the UK.

Clinical expert opinion: *None of the injectable compounds used for passive faecal incontinence have shown lasting effect. It is thought this may be due to migration of the injectable. This device is more likely to remain where placed and therefore may have longer lasting results. Experts were concerned about long term problems of implanted material such as infection and erosion. The company are currently offering free trials. But there needs to be a proper RCT to show clinical and cost effectiveness, using scores for incontinence and quality of life.*

Geko™

Firstkind Ltd has developed Geko™, which is currently in clinical trials for faecal incontinence. It is a self-adhesive, disposable battery powered patch device for transcutaneous posterior tibial nerve stimulation, intended for patient use. It is already CE marked for use in the prevention of venous thromboembolism, oedema, wound healing and limb ischaemia.

Clinical expert opinion: *Not a novel technology, merely a novel way of delivering electrostimulation without needling nerves. Technology for sacral nerve stimulation for faecal incontinence is established. Trials suggest percutaneous posterior tibial nerve stimulation is more efficacious than a transcutaneous approach. However the costs to healthcare and the patient are far greater when patients are required to attend hospital every week for 12 weeks, rather than self-administering a treatment at home. Needs further evaluation.*

Bladder and Bowel Foundation opinion: *Patients and clinicians report variable success with a variety of approaches in terms of transcutaneous posterior tibial nerve stimulation. Auricular acupuncture and traditional acupuncture with needles has been reported as successful by some patients, and could be argued to be a more cost effective approach. Patients report being keen to try non-invasive therapies.*

FENIX® Continence Restoration System

Torax Medical Inc developed FENIX® a magnetic sphincter for faecal incontinence. FENIX® is an alternative to current artificial sphincters and does not require further adjustment or activation devices. A sizing tool ensures the correct device is fitted. The device is placed around the anal sphincter and consists of a ring of titanium beads acting to reinforce the sphincter. The beads have magnetic cores, when closed FENIX® should reduce or stop involuntary passage of stool. Voluntary passage of stool provides sufficient pressure to temporarily break the magnetic bond allowing voiding. The procedure requires a single incision and can be done in approximately 1 hour. It was CE marked in November 2011 and the first devices were implanted in the UK in 2012. The NIHR Horizon Scanning Centre has produced a briefing on FENIX®.

Clinical expert opinion: *Trials are underway and low numbers have been implanted in the UK so far. This is likely to be only for those with end stage faecal incontinence. The history of artificial sphincters is not good; they have had high infection and device complication rates. This device relies solely on magnetic beads and implantation is relatively easy. There will be worries about infection and late extrusion.*

Bladder and Bowel Foundation opinion: *An exciting development for sufferers of faecal incontinence.*

TOPAS

American Medical Systems have a range of slings for male and female urinary incontinence and artificial sphincters for both urinary and faecal incontinence. They have also developed a sling for faecal incontinence in women. TOPAS is a transobturator synthetic mesh sling which provides support to weakened pelvic floor muscles and thereby maintains continence of the bowel. It is in clinical trials in the US (ongoing study with 152 participants, estimated primary completion April 2014).

Clinical expert opinion: *Trying to recreate the puborectalis sling has waxed and waned in popularity over the past 30 years. However placement of synthetic meshes for prolapse and pelvic floor surgery has infection and erosion risks, this will limit the progression of meshes for surgery in the pelvis. Most surgeons would use alternate treatments for faecal incontinence.*

Bladder and Bowel Foundation opinion: *Patients would be extremely cautious in view of the wide negative publicity surrounding meshes and slings. The B&BF helpline receives numerous calls from women with symptoms post mesh insertion for urinary incontinence.*

6. CONTAINMENT TECHNOLOGIES FOR INCONTINENCE

6.1 URINARY INCONTINENCE

Containment technologies are used whilst awaiting successful intervention or where interventions are unsuccessful, unsuitable or undesirable. A range of different products are available from absorbent pads, urinals, sheath appliances and toileting aids, to catheters (either intermittent urethral, indwelling urethral or indwelling suprapubic catheters) and external collecting devices depending on patient circumstances, dexterity and preference.

6.2 FAECAL INCONTINENCE

Similar to urinary incontinence, containment strategies are used while awaiting intervention or where interventions are unsuccessful, unsuitable or undesirable. A range of products are available, including: absorbent body worn and bed pads, anal plugs, and cleansing and barrier products.

6.3 CHANGING AND NOVEL APPROACHES

Containment products

Technology developments for containment products aim to develop more effective and more acceptable products for patients. Key developments focus on new materials to improve absorbency and reduce bulk of both disposable and reusable/washable products, better understanding of skin care and protection, and reducing infection associated with catheters[17].

Telemonitoring

Many healthcare areas are seeing an expansion in telecare and telemonitoring technologies. A range of enuresis alarms and other incontinence alarms using moisture or odour sensors are available. Newer approaches use wireless technology to link incontinence sensors to integrated care systems for use in residential homes to aid response to incontinence and other care events. A range of products are available and

used in Australia[18] and the US. It is unclear how widely adopted this technology is in the UK.

Clinical expert opinion: *Experts felt these systems had potential value for care homes and long term institutionalised elderly patients. Adoption would depend on cost. Some thought sensor technology could assist with a period of bladder retraining.*

Bladder and Bowel Foundation opinion: *It is imperative that we move away from a one pad suits all and 3 pads a day culture. Common sense dictates that if the right product is chosen for an individual then they are likely to use fewer items and also less likely to develop complications as a result of poor continence management, e.g. skin breakdown. Telehealth could play a role in assisting with inventory management and identifying a pad that is fit for purpose.*

7. SUMMARY OF INNOVATION

This review identified a range of technologies representing both incremental developments of established technology groups and novel approaches. Twenty-three new and emerging technologies for incontinence were identified: two for diagnosis, six pharmacological therapies and 15 other therapeutic technologies. Clinical experts advised on the degree of innovation, potential impact, current usage, and barriers to adoption. The Bladder and Bowel Foundation provided helpful insights into the technologies identified from a patient and carer viewpoint.

Bladder diaries are central to diagnosis and assessment of incontinence, newer electronic versions may improve the reliability and accuracy of data and improve self-care. Patients would welcome any developments that make diary completion more user-friendly and easier to fit into busy lives. There have been a range of incremental developments to existing drug classes, aiming to improve their selectivity and delivery, and to reduce problematic side effects. Experts highlighted the combination of agonists with antagonists as a novel and interesting development. A number of new drug classes are in development for urinary incontinence which may widen future treatment options. The B&BF expressed concern that access to alternative treatments may be limited by cost, without taking sufficient account of the wider benefits to quality of life. Ongoing research into biomarkers and improving our understanding of the pathophysiology of incontinence is likely to lead to further drug developments. The development of effective drugs for faecal incontinence is less advanced, but would have the potential for significant impact through providing cheaper treatment and less invasive options than current therapies.

A wide range of devices are currently available to treat both faecal and urinary incontinence. Injectable bulking agents, slings and artificial sphincters have seen incremental developments aiming to improve patient outcomes. Some novel technologies were also identified. Clinical experts were particularly interested in the potential of regenerative medicine in the future treatment of both urinary and faecal incontinence and novel toxins such as senrebotase may offer a future alternative to botulinum toxin injections for OAB. However, patients are increasingly wary of devices for the treatment of incontinence following concerns over meshes and slings, which

may impact the further development and adoption of slings for male urinary incontinence and for faecal incontinence.

Newer out-patient procedures for incontinence, such as Lyrette™ transurethral SUI system, Solace Balloon Delivery System™ and Surinate® Bladder Management System, appear to be novel, though experts were sceptical about their potential efficacy.

Most of the novel health technologies identified in this review are at an early stage of development. Further well designed trials and the collection of cost effectiveness data are required before these can be considered for adoption in clinical practice. The B&BF emphasised the importance of considering the wider benefits to patients and society when making these decisions.

8. REFERENCES

1 Abrams P, Cardozo L, Khoury S et al. Incontinence. 4th International consultation on incontinence. Paris: The International Incontinence Society; July 2008

2 National Institute for Health and Clinical Excellence. Urinary incontinence in women. NICE guidance CG171. London: NICE; September 2013

3 National Institute for Health and Clinical Excellence. Lower urinary tract symptoms. NICE guidance CG97. London: NICE; May 2010

4 National Institute for Health and Clinical Excellence. Faecal incontinence. NICE guidance CG49. London: NICE; June 2007

5 Bhide AA, Cartwright R, Khullar V et al. Biomarkers in overactive bladder. International Journal of Urogynaecology 2013; 24: 1065-1072.

6 National Institute for Health and Clinical Excellence. Mirabegron for treating symptoms of overactive bladder. NICE technology appraisal guidance TA290. London: NICE; June 2013

7 EU Clinical Trials Register. Multicentre, randomised, double-blind, parallel group confirmatory Phase III study to compare the efficacy and safety of cizolirtine citrate 300mg bid. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2004-001116-31 Accessed 7 November 2013.

8 US Food and drug administration website. Products and medical procedures: Urogynaecologic surgical mesh implants. Online article. http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/default.htm Accessed 7 November 2013.

9 Medicines and Healthcare Products Regulatory Agency website. Vaginal tapes for stress urinary incontinence: information for healthcare professionals. Online article http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice%E2%80%93M%E2%80%93T/Syntheticvaginaltapesforstressincontinence/Informationforhealthcareprofessionals/index.htm#2 Accessed 19 November 2013.

10 National Institute for Health and Clinical Excellence. Single incision sub urethral short tape insertion for stress urinary incontinence in women. NICE interventional procedure guidance IPG262. London: NICE; May 2008.

11 National Institute for Health and Clinical Excellence. Intramural urethral bulking procedures for stress urinary incontinence in women. NICE interventional procedure guidance IPG 138. London: NICE; 2005

12 National Institute for Health and Clinical Excellence. Percutaneous posterior tibial nerve stimulation for overactive bladder syndrome. NICE interventional procedure guidance IPG362. London: NICE; October 2010.

13 Zoltan E, Te A. Male slings past present and future. Issues in incontinence. Online article. Laborie. http://www.laborie.com/articles/male-slings-past-present-and-future. Accessed 7 November 2013.

14 Chung E, Ranaweera M, Cartmill R. Newer and novel artificial urinary sphincters (AUS): the development of alternatives to the current AUS device. British Journal of Urology International 2012; 110 supplement 4: 5-11

15 Hussain ZI, Lim M, Stojkovic SG. Systematic review of perianal implants in the treatment of faecal incontinence. British Journal of Surgery 2011; 98: 1526-1536.

16 National Institute for Health and Clinical Excellence. Stimulated graciloplasty for faecal incontinence. NICE interventional procedure guidance IPG159. London: NICE; March 2006

17 Lekan-Rutledge D, Doughty D, Moore KN, Wooldridge L. Promoting social continence: products and devices in the management of urinary incontinence. Online article. Medscape. http://www.medscape.com/viewarticle/467797_1 Accessed 7 November 2013.

18 Fish P, Traynor V. Sensor technology: a smart way to manage continence. Australian Journal of Dementia Care 2013; 2: 35-37. http://twilight.org.au/wp-content/uploads/2013/08/SensorTechnology-aSmartWayToManageContinence.pdf Accessed on 7 November 2013

APPENDIX 1

Statement of conflicts of interest (COI)

Mr Zaki Almallah states he has acted as consultant/advisor to NICE, Cystitis and Overactive Bladder (COB) Foundation, and Astellas, he had acted as lecturer/trainer for the COB Foundation, Astellas, Pfizer and American Medical Systems, he has undertaken research for Astellas and NICE HTA, provided educational support to Astellas and used devices from American Medical Systems, Boston Scientific and Cook Medical.

Mr Mark Chapman states he is Chair of specialised colorectal National Clinical Reference Group.

Professor Christopher Chapple states he is a speaker for Ranbaxy, a Consultant for American Medical Systems, Lilly and ONO, and a consultant, researcher, speaker and trial participant for Allergan, Astellas, Pfizer and Recordati.

Professor Alan Cottenden states he is on the board of trustees of the UK Bladder and Bowel Foundation and the advisory board for the US Simon Foundation for Continence, he sits on the Engineering in Medicine and Health Division of the Institute of Mechanical Engineers and on the editorial of their Journal Engineering in Medicine. He has consulted or received honoraria, research funds or educational grants from Astellas, Hollister, BASF, Lenzing, SCA and Simavita.

Ms Karen Nugent states no conflicts of interest.

Mr Nikesh Thiruchelvam states he participates in NIHR funded clinical trials, trials for Astellas and Pharmalys and sits on the Advisory Board for Astellas.

Professor Douglas Tincello states he is Vice Chairman of the Wellbeing of Women Research Advisory Committee, NIHR Specialty Group lead for reproduction for his area, a member of the NIHR College of Experts, principal investigator on several clinical trials, acted as investigator and/or advisory board member for clinical trials by Eli Lilly &Co, and Ethicon Inc (Johnson & Johnson Medical), he has also been involved in studies receiving grants from Astellas Pharma, ucb Pharma, and Ethicon Inc, he has received paid consultancies from Ethicon and Allergan.

Mr Philip Toozs-Hobson states he has done consultancy work for Allergan and Astellas and received travel help from Astellas.